COMPARATIVE STUDY OF THERAPEUTIC EFFICACY OF PUVA, NBUVB AND PUVASOL IN THE TREATMENT OF CHRONIC PLAQUE TYPE PSORIASIS

Dissertation Submitted in

Partial fulfillment of the University regulations for

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DERMATOLOGY, VENEREOLOGY AND LEPROSY
(BRANCH XX)

MADRAS MEDICAL COLLEGE

THE TAMILNADU DR.M.G.R. MEDICAL UNIVERSITY
CHENNAI, INDIA.

APRIL 2013

CERTIFICATE

Certified that this dissertation titled **"COMPARATIVE STUDY OF THERAPEUTIC EFFICACY OF PUVA, NBUVB AND PUVASOL IN THE TREATMENT OF CHRONIC PLAQUE TYPE PSORIASIS"** is a bonafide work done by **Dr.R.AKILA,** Post graduate student of the Department of Dermatology, Venereology and Leprosy, Madras Medical College, Chennai – 3, during the academic year 2010 – 2013. This work has not previously formed the basis for the award of any degree.

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DECLARATION

I, **Dr.R.AKILA** solemnly declare that this dissertation titled "**COMPARATIVE STUDY OF THERAPEUTIC EFFICACY OF PUVA, NBUVB AND PUVASOL IN THE TREATMENT OF CHRONIC PLAQUE TYPE PSORIASIS**" is a bonafide work done by me at Madras Medical College during 2010-2013 under the guidance and supervision of **Prof. K.MANOHARAN, M.D.,D.D.,** Professor and head of the department of Dermatology, Madras Medical College,Chennai-600003.

This dissertation is submitted to The Tamil Nadu Dr.M.G.R.Medical University, Chennai towards partial fulfillment of the rules and regulations for the award of **M.D Degree in Dermatology, Venereology and Leprosy (BRANCH – XX)**

PLACE :

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(Dr. R.AKILA)

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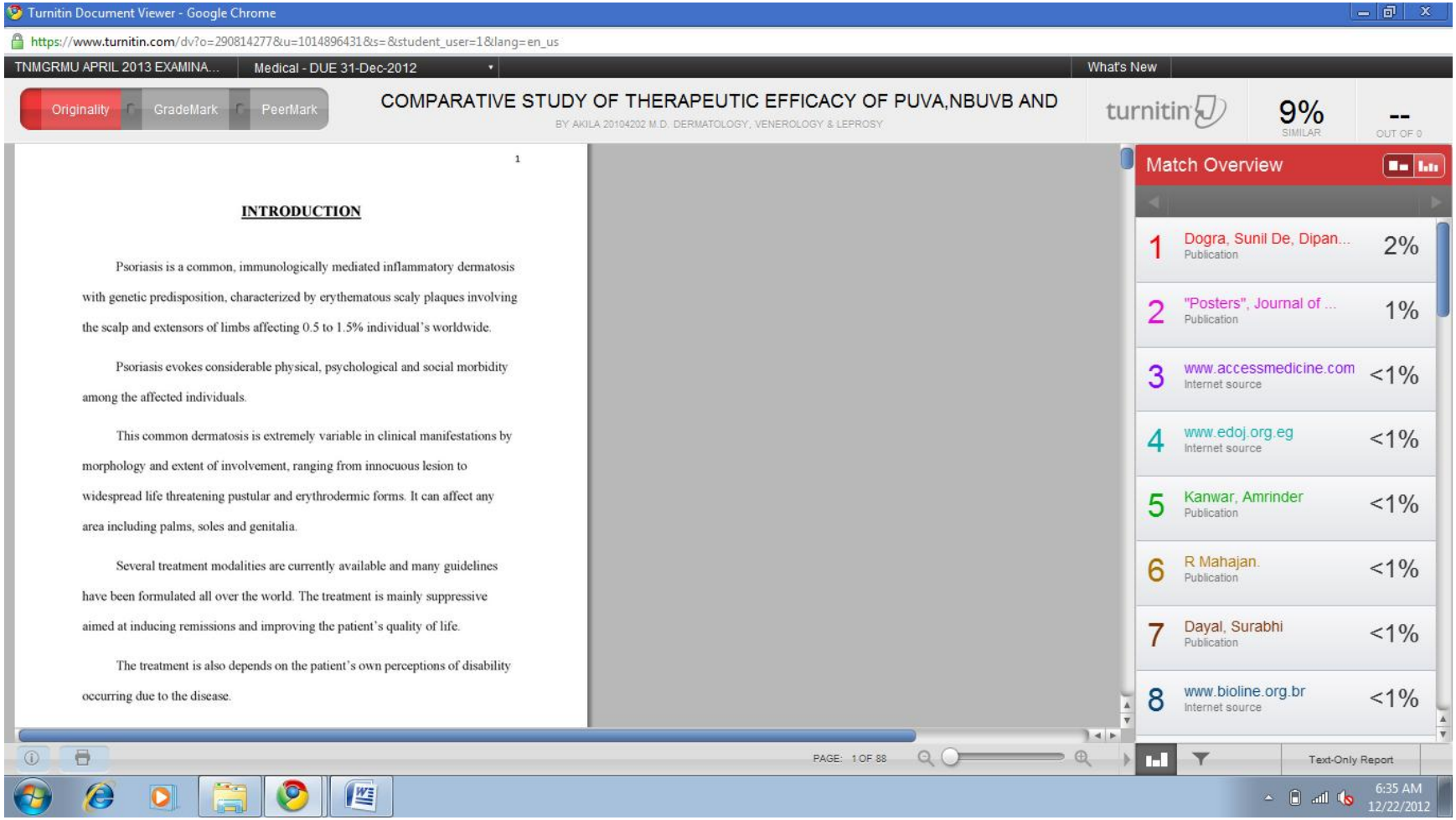
CONTENTS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INTRODUCTION
Psoriasis is a common, immunologically mediated inflammatory dermatosis with genetic predisposition, characterized by erythematous scaly plaques involving the scalp and extensors of limbs affecting 0.5 to 1.5% individual's worldwide.
Psoriasis evokes considerable physical, psychological and social morbidity among the affected individuals.
This common dermatosis is extremely variable in clinical manifestations by morphology and extent of involvement, ranging from innocuous lesion to widespread life threatening pustular and erythrodermic forms. It can affect any area including palms, soles and genitalia.
Several treatment modalities are currently available and many guidelines have been formulated all over the world. The treatment is mainly suppressive aimed at inducing remissions and improving the patient's quality of life.
The treatment is also depends on the patient's own perceptions of disability occurring due to the disease.
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INTRODUCTION

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Routinely for limited plaque psoriasis coal tar, topical corticosteroids, dithranol, calcipotriol and topical photochemotherapy are administered.

For extensive psoriasis UVB, PUVA, PUVASOL, methotrexate, hydroxyurea, acitretin and cyclosporine are preferred.

Disease modifying agents such as etanercept, infliximab and other biological may be required in resistant cases.

This study was designed to compare the therapeutic efficacy of PUVA, PUVASOL and NBUVB in the treatment of chronic plaque type psoriasis involving more than 20% body surface area.

HISTORICAL REVIEW

Psoriasis is a disease of the skin, characterized by a chronic relapsing and variable clinical features. The cutaneous lesions are so distinct there by a clinical diagnosis is easy to make.[1] Psoriasis is a polygenic disease. Various triggering factors such as infections, trauma, medications, may elicit a psoriatic phenotype in a predisposed individual.[2]

The earliest description of psoriasis is given at the beginning of medicine in the Corpus Hippocraticum. This work was edited in Alexandria 100 years after the death of Hippocrates (460-377 BC). [3]

Hippocrates used the term “psora” and “lepra” for conditions, recognized as psoriasis. [1]

The original description of psoriasis is attributed to Celsus in 35 to 40 AD. During Biblical times and there after psoriasis was confused with syphilis, leprosy and other skin diseases.

In the second century AD the term “psoriasis” was introduced by Galeo. He described an itchy skin condition characterized by scaling of the eyelid, scrotum and corner of the eyes. [2]

In 1808, Robert Willan an English physician made the first description of psoriasis and its different manifestations. [4]

In 1841, Hebra definitely separated the clinical features of psoriasis from that of leprosy.

Robert William (1757-1812) was the first person to describe psoriasis as a clinical entity. He described psoriasiform lesions as two different groups,

1. Discoid lesion - “Lepra Graecorum”
2. Polycyclic confluent lesion - “Psora Leprosa”

The later is called as psoriasis. [1]

1n 1841, a Viennese physician Ferdinand Von Hebra provided a complete precise description of psoriasis.

Heinrich Auspitz (1835-1886) called attention to the bleeding points on removal of scales, which is a characteristic sign of psoriasis known today by his name. [5]

In 1876, Heinrich Koebner described koebner’s phenomenon, a most significant observation on the natural history of psoriasis. [6]

Exposure to sunlight is the oldest treatment for psoriasis. [2] In 1878, a British dermatologist Balmanno squire introduced the chrysophonic acid ointment(chrysaeobin) for the treatment of psoriasis.

In 1895, Sir Jonathan Hutchinson described the rupial form of psoriasis and the use of Fowlers solution in the treatment of psoriasis.

In 1898, Munro described the microabscess of psoriasis which today bears his name.[7] In 1910, Leovan Zumbusch described generalised pustular psoriasis which is known as Von Zumbusch disease. [8]

In 1916, Pau Gerson Unna,established the use of anthralin in the treatment of psoriasis. [9] In 1925, Goeckerman reported the combination therapy of crude coal tar with UV B irradiation. [10]

In 1926, a Russian dermatologist Woronoff immortalized in the psoriatic literature for description of a pale zone around a plaque of psoriasis referred to as “Woronoff”s ring”. [11]

In 1927, Frank kogoj of Yugoslavia described the spongiform pustule. [12] In 1950, Philip Hench received Noble prize for the discovery of cortisone.

In 1951, Gubner was the first to use Aminopterin for the treatment of psoriasis. Later it was replaced by its more stable analogue Methotrexate. [13]

In 1953, John Ingram established the dithranol regimen and first day care centre for psoriatic patients. [14] In 1970, Leavell reported the use of hydroxyurea in the treatment of psoriasis.

In 1974, Parrish J.A.et al reported the combined use of 8-methoxypsoralen and UV A in psoriasis.They coined the term photochemotherapy and acronym “PUVA”. [15]

In 1976, Fischer demonstrated the effect of UVB alone in the treatment of psoriasis.[16] In 1982, first use of Methotrexate and UV B reported. [17]

In 1980, Parrish and Jaenicke demonstrated that wavelength near 313 nm were most efficient for clearing psoriasis. [18] In 1986, Morimoto reported the use of topical calcipotriol , which is an vitamin D metabolite in the treatment of psoriasis.

And for this century(2000),more technological treatments discovered such as Biological and Laser treatments.

PSORIASIS-QUANTUM OF PROBLEM:

Psoriasis is universal in occurrence.The prevalence of psoriasis varies from 0.1 to 2.84 % in different epidemiological and clinical studies. [19]

The incidence ranges from 0.3% in China,1.4% in US 2.3% in Sweden and 2.8 % in Faroes. [20]

In India the incidence ranges from 0.8-5.6% in dermatology clinics and Hospitals. Psoriasis is rare in West African and North American Blacks. [21-25]

The age of onset of psoriasis varies. In two studies the highest incidence was in the age groups of 15-45 years and 11-40 years.[19] Females develop psoriasis earlier than males. [26]

In 1986, Kaur reported the mean age of onset for males and females were 36.9±15.10 and 29.34±15.10 years respectively. Greater is the probability of a family history of psoriasis when the onset is earlier. [27]

In most Indian studies, a higher prevalence is noted in males(2.4%) than in females(0.8%).[22,23] In 1967, Hellgren in a study of 39000 subjects found that 6.4% of the relatives of psoriatic patients has psoriasis.

There are two clinical presentations of psoriasis.

Type 1 disease (Hereditary form) and type 2 disease (Sporadic form). Type 1 disease is more common and it is associated with HLA CW6 with more severe and recurrent course. Type 2 disease starts later in life without any family history or HLA CW6 association.

ETIOLOGY AND PRECIPITATING FACTORS:

The cause of psoriasis is not fully understood.But there are many factors that precipitate psoriasis.They are

1. Trauma:

Psoriatic lesion may occur at the sites of injury to the skin as a koebner phenomenon.The trauma may be physical, chemical, mechanical or allergic.

2. Infection:

In children with guttate psoriasis,56-85% have precedent evidence of streptococcal infection like upper respiratory infection or tonsillitis. [28] HIV infection is associated with exacerbation of psoriasis.

3. Season:

Sunlight and hot weather are reported to be beneficial, while cold weather exacerbates psoriasis. [29]

4. Metabolic factors:

Hypocalcemia and dialysis have precipitated psoriasis. [30]

5. Endocrine factors:

There are peaks of incidence of psoriasis at puberty and at menopause. Remission of psoriasis occur during pregnancy and there is exacerbation during the post partum period. [31]

6. Psychogenic factors

Stress may exacerbate psoriasis. The disease can cause ‘depression’ in the patient, which further exacerbates psoriasis. [32]

7. Alcohol:

Alcoholics who have psoriasis, drink excessive amounts of alcohol and subsequently have a flare of disease. [33]

8. Anatomic sites:

In chronic stationary psoriasis, the scalp is most frequently involved, followed by knees and elbows. In guttate psoriasis, the proximal extremities and trunk are affected. [34]

9. Drugs:

Administration of lithium, beta blockers, antimalarials, clonidine, amiodarone, potassium iodide, digoxin, gemfibrosil, terfenadine, trazodone, penicillin, NSAIDS and sudden withdrawal of systemic steroids can exacerbate Psoriasis. [35]

PATHOGENESIS

The literature of recent years contains a vast array of investigative observations and data relating to the pathogenesis. While still inconclusive, they emphasize the complexity of the disease process and broaden our understanding of clinical features, course and treatment of the disease.

1) Epidermal kinetics :

The epidermal proliferation in psoriasis was described by Van Scott and Ekel (1963). There is shortening of the epidermal germinative cell cycle, an increase in the number of cells in the proliferative pool and shortening of the epidermal turnover time in psoriatic lesion. Epidermal proliferation and epidermal growth factor (EGF) receptor expression appears to be increased in psoriatic lesion.[36]

2) Leucocyte attractants:

The presence of dermal and intra-epidermal neutrophil infiltrates in psoriatic lesions suggests that one or more neutrophil attractants are released locally. The neutrophil attractants recovered from psoriatic lesion include leucotriene B4 (LTB4), monohydroxy arachidonic acid metabolite, 12 (R) hydroxyl-5, 8, 10, 14eicosatetraenoic acid (12 [R] – HETE), ether-linked phospholipid, platelet activating factor, interleukin 8 or neutrophil activating peptide (NAP) and the complement product C5 a des arg.

3) Polyamines:

Polyamines are low molecular weight organic amines. Polyamines like spermidine, spermine and putrescine are involved in DNA synthesis and cell proliferation. Antipsoriatic agents such as topical steroids, anthralin, PUVA and retinoids have been found to reduce epidermal polyamine synthesis.

4) Cyclic Nucleotides:

Increased levels of cAMP cause inhibition of cell activity, whereas increased cGMP levels may be stimulatory. Alterations in cGMP / cAMP ratios are therefore considered to be of possible importance in the genesis of the hyperproliferative changes in psoriasis.

5) Proteinases:

Proteinases like plasminogen activator and various cathepsin and their inactivating antiprotease like alpha-1 antitrypsin may play a role in epidermal proliferation and differentiation.

6) Immunological Mechanism:

Following trauma or infection, vasodilation occurs and is accompanied by an influx of neutrophils into the epidermis. Proteolytic enzymes released by neutrophils unmask the stratum corneum antigen. Stratum corneum antibodies leak into the epidermis and fix the newly

exposed antigen. The antigen-antibody reaction triggers the complement cascade and further inflammatory response.[37]

Normally basal cell nuclear material is not recognized by the immunological system. A genetic defect or a virus leads to malfunctioning of such a clone of suppressor cells leading to recognition of basal cell nuclear material as antigen.

Subsequently antibodies are formed against this antigen leading to immunological response which results in epidermal cell proliferation.

CLINICAL CLASSIFICATION:

1. Chronic plaque psoriasis
2. Guttate psoriasis
3. Erythrodermic psoriasis
4. Pustular psoriasis
5. Psoriasis unguis
6. Mucous membrane psoriasis
7. Psoriatic arthritis
8. Regional variations:

   Scalp, face, flexures, scrotum, napkin area, palms and soles.

9. Follicular psoriasis

10. Rupioid , Elephantine and Ostraceous psoriasis

11. Unstable psoriasis

12. Atypical forms:

    a. Linear and Zonal forms

    b. Sebopsoriasis

    c. Ocular lesions.

AUSPITZ'S SIGN:

Auspitz's sign - when psoriatic scales are scrapped with a glass slide punctate bleeding points appears . This was described by Heinrich Auspitz.

SEVERITY:

Psoriasis is usually graded as mild (less than three percent of the body), moderate (three to ten percent of the body) or severe (more than ten percent of the body). [38]

Degree of severity is generally based on:

1. Proportion of BSA affected

2. Activity of lesions as evidenced by extent of scaling, thickness and redness

3. Therapeutic response to prior treatment

4. Impact of disease on individual.

PHOTOCHEMOTHERAPY:

PUVA THERAPY:

Psoralen is used topically or taken orally to sensitize the skin, then the skin is exposed to UVA.

Photo chemotherapy (PUVA) using psoralen and high intensity long wave ultra violet rays is an effective treatment for chronic plaque psoriasis.

SPECTRUM OF ELECTROMAGNETIC WAVES: [39]

Infra red rays and radio waves	> 700 nano meter
Visible light	400 – 700nano meter
Ultra violet A	320 – 400 nano meter
Ultraviolet B	280 -320 nano meter
Ultra violet C	100 -280 nano meter

Gamma & Cosmic rays < 100 nano meter

EFFECTS OF ULTRAVIOLET RADIATION ON SKIN [40]

Photobiological reactions occurs by interaction of light with the skin.

Photobiological reactions takes place in several steps.

STEP 1:Absorption of light by chromophore.

Light has to be absorbed by molecules, such as proteins or DNA, which is known as chromophores. Absorption spectrum of the chromophore is the specific wavelength of the light absorbed by each chromophore. Absorption maxima of the chromophore is the wavelength which has the greatest probability of absorption.

STEP 2 : Excitation to singlet/triplet state

Chromophore gets excited into singlet and triplet states after absorption of light.

STEP 3 : Formation of photoproduct

Triplet state initiate a chemical change in the chromophore there by transforming it into photoproduct.

STEP 4 : Initiation of biochemical reactions

The photoproducts may initiate a complex biochemical reactions such as induction of gene products, enzymatic repair and DNA replication.

STEP 5 : Cellular response

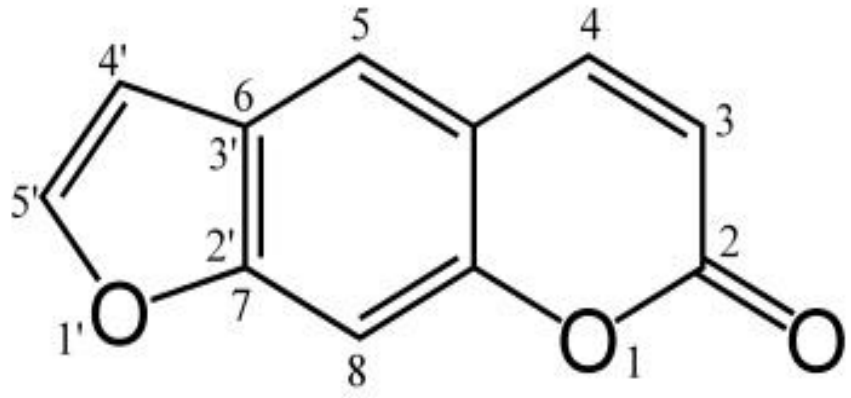
Above mentioned biochemical reactions culminate in a cellular responses such as apoptosis, mitosis and differentiation.

STEP 6:Clinical response

The final step of photobiological reaction is the clinical manifestations in the form of hyperplasia, erythema, formation of tumour etc.

PSORALEN:

Psoralen belongs to the family of Furocoumarins and it is the parent compound too. The furan ring common to Psoralen and Coumarins makes them structurally related. Psoralen occurs naturally in the seeds of psoralea corylifolia (Indian plant) , ammi majus (Egyptian plant) as well as in the fig, celery, parsley, west Indian satinwood and cloves. [41]



The medical use of these plants in the treatment of vitiligo by ancient Egyptians dates back to 1500 B.C and by Indians to1400B.C.

CHEMISTRY:

Psoralen commonly used in photochemo therapy is 8-methoxypsoralen (xanthotoxin, Methoxsalen) Which is a plant product. Synthetic preparations are available , as 4-5-8 trimethyl psoralen (trioxsalen, TMP) and it is less phototoxic. Newer psoralens are 5 methoxy psoralen (bergapten, angelicin). [42] Photobiological activity of angelicin is low. [43]

PHARMACOLOGY:

When taken orally, 8 methoxypsoralen is absorbed from the G.I.T. One hour after intake the photo sensitiveness starts, reaching peak at about two hours and photosensitive effect wears off after about eight hours. [44]

After oral administration the drug is metabolized in the liver by hydroxylation and glucuronide formation. More than 90% of the drug is excreted in the urine with in 12 hours. [45]

The half life of Methoxsalen is one hour. It is excreted rapidly which helps in preventing photosensitivity. [46]

Unique features of psoralen pharmacology are

1. Insolubility in water
2. Physical formulation influences absorption
3. Food decreases absorption
4. First-pass effect through liver and
5. Large interindividual variation in absorption.

Dietary influences may be important as a fat rich meal may delay or reduce the absorption of 8-MOP. [47]

MECHANISM OF ACTION: [48]

Psoralen causes photosensitization of skin by two different reactions. When skin is exposed to ultraviolet A light after intake of Psoralen following reactions occur.

1. TYPE 1: Anaerobic , which does not require O_2 and site of cellular damage is deoxy ribonucleic acid.

2. TYPE 2: Sensitized dependent, involves formation of reactive O_2 species such as O_2, O_2^- and free radicals.

In these modes of reactions, reactive form of Psoralen is in the triplet state.

The sites of reaction are:

1. DNA & chromatin

2. Epidermal, dermal and endothelial cell membranes.

3. RNA, lysosomes, enzymes in cytoplasm of cells.

4. Membrane lipids involving a photodynamic reaction.

Major photochemical reaction of Psoralen is formation of mono and bifunctional adducts with pyrimidine bases in the DNA, which inhibits Deoxy riboneucleic acid synthesis and multiplication of cells.

Psoralen ultraviolet A therapy affects cells like the T lymphocytes or neutrophils which play important role in pathology of Psoriasis. Following PUVA treatment a decrease in number of Tlymphocytes has been reported. [49]

INDICATIONS: [50]

1. Psoriasis
2. Vitiligo

3. Atopic dermatitis
4. Cutaneous T cell leukemia
5. Lichen planus
6. Urticaria pigmentosa
7. Graft versus host disease
8. Actinic prurigo
9. Nodular prurigo
10. Pityriasis alba
11. Preventive treatment for photosensitive dermatoses like :

    a. Polymorphic light eruption

    b. Chronic actinic dermatosis

    c. Solar urticaria

    d. Hydroa vacciniforme

    e. Persistent light reaction

12. Miscellaneous:

Alopecia areata, acute and chronic pityriasis lichenoides, lymphomatoid papulosis and pityriasis rubra pilaris.

PROCEDURE: [48]

0.6-0.8mg/kilogram body weight of 8-Methoxy Psoralen is administered orally, and after 1 to 3 hours whole body is irradiated with

Ultra violet A. According to skin typing or photo toxicity testing initial dose of UV A is predetermined.

Repeated exposures are necessary for clearance of the disease, if pigmentation appears UV A doses have to be increased.After achievement of satisfactory clearance of the disease dosage is reduced. The last UV A dose is the maintenance dose.

PROTOCOL FOR PUVA THERAPY:

Since the introduction of PUVA therapy in 1974,there are numerous protocols have been used. They all are slightly different, but share the same principle of repeated and regular PUVA exposures.

All these protocols have 2 phases:

1. Clearance phase aiming at suppression of the disease.
2. Maintenance phase by tapering to a minimum dose of therapy to maintain and extend remission.

Two protocols which are commonly used are

1. American protocol
2. European protocol

AMERICAN PROTOCOL: [51]

The first exposure dose of therapy depends on the skin typing and it is twice or thrice per week. Depending on the erythema production and therapeutic response dose increments ranges from half to one and half joules per square centimeter area.

EUROPEAN PROTOCOL: [52]

First minimum phototoxic dose (MPD) has to be determined then treatment is administered and the MPD is the patient's initial UV A dose. Four treatments are given per week. In a week first two days therapy is given, followed by rest on third day. Again therapy should be given on fourth and fifth day. In the absence of development of erythema after four treatments dose increment is performed in a range from half to two joules per square centimeter area.

	AMERICAN	**EUROPEAN**
Initial dose determination	Skin phototype	MPD
No.of weekly treatments	2	4
Increments	Predetermined and fixed	Individualized and flexible
No. of weeks required for clearing	12.7	5.7
No. of exposures	25	20
Cumulative UVA dose	245J/ cm^2	96 J/ cm^2

SKIN PHOTOTYPES: [53]

1 Burns always, never tans

2 Burns always, tans sometimes

3 Sometimes burns, tans always

4 Never burns, but tans always

5 Moderate pigmentation

6 Deep pigmentation

Types 1 – 4 are determined by history and

Types 5 – 6 by physical examination..

Dose of UVA radiation for induction phase schedules [54]

Skin type	UVA radiation dose J/ cm^2		
	Initial dose	Increments	Maximum dose
1	0.5	0.5	8
2	1.0	0.5	8
3	1.5	1.0	12
4	2.0	1.0	12
5	2.5	1.5	20
6	3.0	1.5	20

Indian skin comes under 4 & 5 phototype and is usual to start with 2.0 J/cm^2 and increments of 0.5 – 1J/cm^2 based on skin response.

MINIMUM PHOTOTOXIC DOSE (MPD):

Minimum phototoxic dose is defined as the lowest dose of UV A delivered to the skin after ingestion of 8-MOP which causes a well demarcated erythema when small test areas of skin is treated with large doses of UV A (0.5 – 5 Joules/centimeter square). After 72 hours of testing, when a peak phototoxicity has reached, erythema readings are performed.

Extra treatment may be needed for the lower limbs, where the lesions respond slower. An additional irradiation of 0.5 – 5 J/cm^2 is needed for these areas, the dose being gradually increased.

Average of about 20 exposures is required for clearing,but varies from 15 – 20. About 5-20 J/cm^2 is the final clearance dose of UV radiation, depending upon the skin type. For all skin types the average cumulative dose of Ultraviolet A needed to clear is 103 & 79 Joules per square centimeter in two European trials. [55]

Considerably higher mean cumulative Ultraviolet A dose (245 Joules per square centimeter) was noted in the US trial. [56]

If no maintenance therapy is given, most of the patients presents with relapse in the first month. In patients for whom maintenance therapy is given and stopped after two to three months, the relapse do not occur immediately. Later group remain symptom free for a period of 6- 12 months.[57]

During PUVA therapy goggles should be worn to protect the eyes. It should be worn for 24 hours after therapy.

During treatment men should protect their genitals from UVA exposure.

MAINTENANCE SCHEDULE FOR PUVA THERAPY:

Four treatments at weekly intervals,then

Four treatments every other week,then

Four treatments every third week,then

Four treatments every fourth week,then

Stop treatment or continue monthly.

CONTRAINDICATIONS: [58]

ABSOLUTE:

1. Pregnancy and lactation

2. Lupus erythematosus

3. Severe hepatic failure

4. Severe renal failure

5. Xerodermo pigmentosum.

RELATIVE:

1. Children < 12 years of age
2. Previous exposure to x rays,arsenic
3. Personal or family H/O melanoma
4. Immuno suppressed patients
5. Cataract
6. Concomitant intake of phototoxic drugs like doxycycline, sparfloxacin etc

SIDE EFFECTS: [59]

SHORT TERM:

1. Erythema
2. Sunburn
3. Pruritis

4. Headache
5. Nausea
6. Koebner’s response
7. Dizziness
8. Drug eruption
9. Severe skin pain
10. Bronchial reaction
11. Contact allergy

LONG TERM:

1. Xerosis
2. Hyperpigmentation
3. Hypopigmentation
4. Photo ageing / Wrinkling
5. Chronic phototoxicity
6. Oedema of legs
7. Hypertrichosis

8. Nail changes like pigmentation, subungual hemorrhage & photo onycholysis

9. Dyskeratotic or precancerous conditions such as Bowen's disease, Keratoacanthoma and Actinic keratosis.

10. Cutaneous malignancy such as squamous cell carcinoma

11. Cataract

12. Malaise

13. Depression

14. Lack of concentration

15. Insomnia

Certain skin conditions such as seborrhoeic dermatitis, lupus erythematosus, bullous pemphigoid and acne are aggravated by PUVA therapy.

There are isolated reports of certain skin conditions linked with PUVA therapy. They are malignant melanoma,hepatotoxicity, nephrotic syndrome, hypotension, lichenoid eruption, leukemia and exacerbation of gouty arthritis.

PUVA MONITORING GUIDELINES: [60]

Baseline

Cutaneous:

Skin examination for actinic damage, premalignant lesions and skin cancer

Skin biopsy of suspicious lesions

Ocular:

Assessment of visual acuity

Gross examination of the eye

Examination of cornea and lens using slit lamp

Fundoscopy of retina.

Laboratory:

If there is positive findings on history or examination, evaluation of renal and/or liver function

If there is history of photosensitivity or other evidence of collagen vascular disease, evaluation for lupus vulgaris

FOLLOW UP

Ocular:

If there are abnormal ocular findings at baseline or subsequently, repeat eye examination yearly or more often

Cutaneous:

Educate the patient to examine monthly for skin cancer

Skin cancer screening of entire skin , at least yearly

NARROW BAND ULTRAVIOLET B THERAPY

NBUVB is one of the novel therapeutic intervention now available in treating several dermatological conditions. Fisher identified that narrow band ultraviolet B radiation which has a wave length of 313 (311±2) nanometer is efficient in clearing lesions. Even higher doses do not produce notable erythema. [61]

Parish Jaenicke identified that clearance of psoriasis is better with wavelength of 313nm. [62]

These observations lead to the invention of artificial fluorescent lamps which contains phosphor (TL-01) .

Van Weelden et al[63] and Green et al[64] used these lamps first in 1988 for treating Psoriasis.

MECHANISM OF ACTION:

1. Absorption of UVB by nucleotides of DNA leads to formation of DNA photoadducts with pyrimidine dimers,which interfere with cell cycle progression and induces growth arrest.
2. Releases prostaglandin which interferes expression and production of interleukins and interferons. [65]
3. Decreases the expression of Interleukin-12, Interleukin-18,Interleukin-23 and Interferon – gamma, by inducing apoptosis.[66]
4. Depletes T cells and NK cell activity.
5. Suppresses antigen presenting cells function.
6. Down regulates Th 17 cells. [67]

INDICATIONS: [68]

1. Psoriasis
2. Vitiligo
3. Atopic dermatitis

4. Pityriasis rosea
5. Generalised lichen planus
6. Parapsoriasis
7. Seborrheic dermatitis
8. Pruritis
9. Mycosis fungoides
10. Pityriasis rubra pilaris
11. Prurigo nodularis
12. Acquired perforating dermatosis
13. Scleroderma
14. For prevention of photodermatoses.

CONTRAINDICATIONS: [69]

1. Patients with photosensitivity.
2. History of exposure to arsenic.
3. History of exposure to ionizing radiation.
4. History of previous melanoma or multiple non melanoma skin cancer.

5. Family history of melanoma

6. Persons with skin type 1

INSTRUCTIONS TO THE PATIENT:

1. Use of protective eye goggles.

2. In male patients shielding genitals

3. Avoiding sun exposure unnecessarily.

PROCEDURE:

On the basis of minimal erythema dose (MED) initial dose is calculated. MED is the lowest dose of UVB producing defined erythema at test site.MED is determined 24 hours after exposure of UVB on the back/buttocks of around 1cm× 1 cm. Initial dose is generally 70% of minimal erythema dose. [70]

Pai et al [71] determined the average MED in skin type 4 is 600 mJ/cm^2 and in skin type 5 is 1100 m J/cm^2 .

MED of 150 m J/ cm^2 to 400 m J/cm^2 is observed by Serish and Srinivas. [72]

According to latest consensus as suggested by American academy of Dermatology, the starting dose is decided by skin type and not based on minimal erythema dose .

Dose recommendations are as follows:

Skin type	**Initial Dose (milli Joules/square centimeter)**	**Dose increments(milli Joules/square centimeter)**
1	130	15
2	220	25
3	260	40
4	330	45
5	350	60
6	400	65

Erythema response is graded as: [73]

1. No erythema
2. Mild erythema –grade 1
3. Moderate and well defined erythema – grade 2
4. Severe painful erythema persisting for > 24 hours –grade 3.

No erythema-Dose is increased by 20 % of last dose.

Grade 1-Previous dose is maintained and subsequent dose increment is reduced to 10 %.

Grade 2-Postpone one treatment, repeat previous dose at next visit and reduce to 10 % increment.

Grade 3-No treatment is offered until recovery and further treatment is given by reducing exposure dose by half and 10 % increment there after.[74]

If MED is calculated, dose increment should be 10 % of initial MED for the initial 20 exposures and as per physicians discretion there after.

Frequency of exposure is thrice or five times per week. [75]

If dose is missed, NBUVB can be restarted.

< 1 week - Maintain the last exposure dose.

1-2 weeks - Restart at a dose < 25 % of the last dose.

2-3weeks - Restart at 50 % depleted dose.

>3 weeks - Restart from the previous starting dose.

In India,approach commonly practiced involves a standard starting dose of 280mJ/cm^2 followed by stepwise increase of 20% depending on the patient's erythema response.

SIDE EFFECTS: [76]

1. Erythema
2. Blistering
3. Pruritis
4. Reactivation of herpes simplex
5. Exposure keratitis and conjunctivitis
6. Tanning

ADVANTAGES OF NB-UVB OVER PUVA THERAPY

1. No need for intake of psoralens. Hence side effects of psoralens can be avoided.
2. Useful in children under 12 years of age, where psoralen is contraindicated.

3. Can be used in pregnancy and lactation, where psoralens are contraindicated.

4. Can be used in elderly or those with poor hepatic or renal function.

5. No eye protection is necessary outside the chamber.

6. Shorter exposure time as compared to PUVA therapy.

PUVASOL THERAPY

Administration of psoralens followed by exposure to sunlight is known as PUVASOL therapy. Trimethoxypsoralen is preferable for PUVASOL therapy. 10 AM to 2 PM is the best time for sun exposure.

MECHANISM OF ACTION

Exact mechanism is not known, but it probably induces a modification in circulating and insitu lymphocyte population. It also decreases thymus dependent lymphocytes. [77]

Here, both UV A & UV B in sunlight result in photoaugmentation and photoaddition. [78, 79] Erythemogenic property of UV A may be additive to subclinical or visible erythema induced by UV B. [80]

During first sitting of therapy exposure to sunlight is limited to 10 minutes. Then duration of exposure can be increased according to the response.

ADVANTAGES:

1. Inexpensive

2. Patient need not travel for treatment

DISADVANTAGES:

1. Quantification of ultraviolet light is difficult.

2. The total dose of UV A that effectively reaches skin varies with the hour of the day, season, latitude and atmospheric conditions.

3. Need for privacy

4. Unnecessary presence of ultraviolet B, visible light and infrared rays may lead to undesirable reactions.

AIM OF THE STUDY

Aim of the study is to evaluate the therapeutic efficacy of

1. PUVA(Psoralen ultraviolet A therapy)

2. NBUVB (Narrow band ultraviolet B therapy)

3. PUVASOL(Psoralen ultraviolet A solar therapy)

in patients with chronic plaque type of psoriasis involving more than 20% of body surface area .

MATERIALS AND METHODS

Sixty patients of chronic plaque type psoriasis who attended the psoriasis outpatient clinic at the Department of Dermatology, Rajiv Gandhi Government General Hospital, Chennai were randomly selected from August 2010 to September 2012.

The diagnosis of psoriasis was made clinically by morphology of lesions and Auspitz sign.

STUDY DESIGN : Prospective study

INCLUSION CRITERIA

Patients with chronic plaque type of psoriasis involving more than 20% of body surface area.

EXCLUSION CRITERIA

1. Photosensitive disorders or history of photo damage
2. Pregnant and Lactating women
3. Children < 12 years of age
4. Previous or family history of malignant melanoma

5. H/O exposure to inorganic arsenic or ionizing radiation

6. Women contemplating conception.

7. Pustular, erythrodermic psoriatic patients

All patients were explained about the disease, benefits and side effects of the treatment were discussed with them.

Informal written consent was obtained from all patients before initiation of treatment.

All patients were evaluated as follows

1. History

2. General examination

3. Systemic examination

4. Dermatological examination

5. Investigations-

   a. Complete hemogram

   b. Urine analysis

   c. Renal function test

   d. Serum calcium, uric acid

e. Liver function test

f. Blood VDRL

g. ELISA for HIV

6. Ophthalmic evaluation

TREATMENT PROTOCOL AND METHODOLOGY

Sixty patients with chronic plaque type of psoriasis involving more than 20% of body surface area were randomly allocated to any one of the following three groups.

Group A: PUVA therapy, Group B: NBUVB therapy, Group C: PUVASOL therapy.

GROUP A: PUVA THERAPY

- 20 patients were included in this group.
- Patients were asked to take Tablet. Trimethoxy Psoralen 20mg in empty stomach 2 hours prior to the exposure of UVA therapy.
- All patients were asked to wear UV goggles when inside the phototherapy unit and throughout the day thereafter.

- Patients were advised to protect their genitalia.
- Initial UVA dose of 0.5 J/cm^2 was started in all patients.
- Patients were advised to expose the affected parts.
- Patients were instructed to come out of the chamber when the light switches off or when alarm beeps or if they became uncomfortable during the treatment either due to burning or stinging sensation of the skin.
- If the initial dose was tolerated, incremental dose of 0.5J/cm^2 at each subsequent visit depending on the patients erythema response.
- Treatment was given twice weekly (Monday and Friday).
- Patients were monitored regularly every week.
- Patients were instructed to report immediately if any of the adverse effects were noted.

GROUP B: NARROW BAND UVB THERAPY

- 20 patients were included in this group.

- All patients were asked to wear UV goggles when inside the phototherapy unit.
- Patients were advised to protect their genitalia.
- Initial UVB dose of 0.25 J/cm^2 was started in all patients.
- Patients were advised to expose the affected parts.
- Patients were instructed to come out of the chamber when the light switches off or alarm beeps or if they became uncomfortable during the treatment either due to burning or stinging sensation of the skin.
- If the initial dose was tolerated, 20% incremental dose was given at each subsequent visit depending on the patient's erythema response.
- Treatment was given thrice weekly on non consecutive days.
- Patients were monitored regularly every week.
- Patients were instructed to report immediately if any of the adverse effects were noted.

GROUP C: PUVASOL THERAPY

- 20 patients were included in this group.
- Patients were asked to take Tablet. Trimethoxy Psoralen 20mg in empty stomach 2 hours prior to the exposure of sunlight.
- Patients were asked to expose the affected area to sunlight for ten minutes preferably between 11 A.M TO 2 P.M.
- Treatment was given thrice weekly on non consecutive days.
- Patients were monitored regularly every week.

FOLLOW UP

Patients were followed up every weekly, and PASI score was calculated at 0, 4, 8, 12 and 16 weeks for all three groups. These were compared and statically analyzed.

EFFICACY ASSESSMENT

Severity and extent of psoriasis were evaluated using “Psoriasis Area and Severity Index” (PASI) score.

Severity of Erythema (E), Desquamation (D) and Induration (I) was recorded on a 5 point scale as follows.

0	Nil
1	Mild
2	Moderate
3	Severe
4	Very severe

The area of involvement was recorded on a 7 point scale as follows

0	Nil
1	<10%
2	10-29%
3	30-49%
4	50-69%
5	70-89%
6	90-100%

PASI was calculated as follows

$$\mathbf{PASI = 0.1(E_H+I_H+D_H)\ AH + 0.2(E_U+I_U+D_U)\ AU +}$$

$$\mathbf{0.3(E_T+I_T+D_T)\ AT + 0.4(E_L+I_L+D_L)}$$

A - Area

H - Head

U - Upper limb

T - Trunk

L - Lower limb

OBSERVATION AND RESULTS

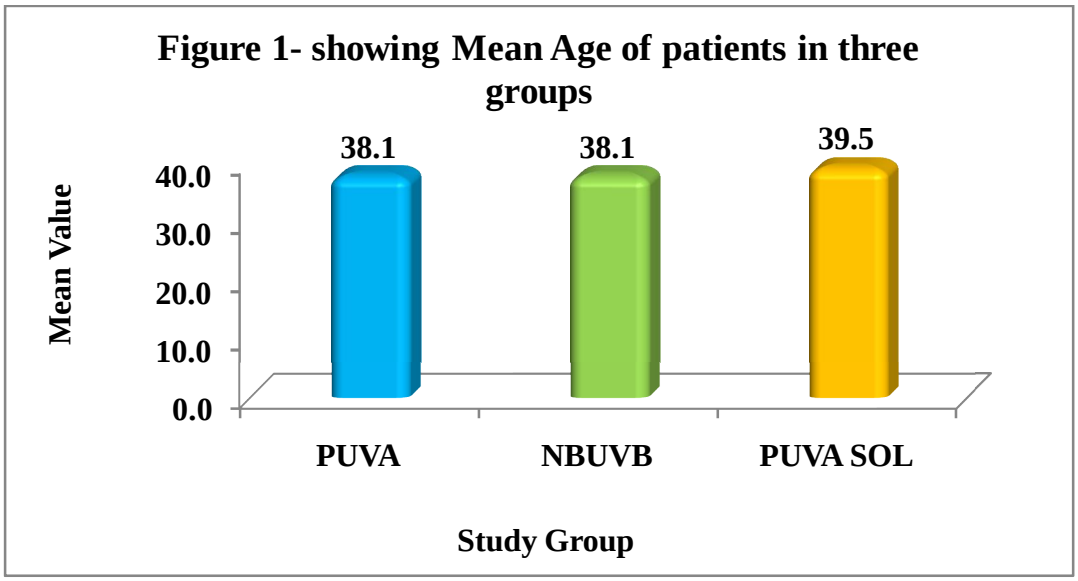
AGE DISTRIBUTION

The mean age in our study group was 38.05 years in PUVA, NBUVB group and 39.45 years in PUVASOL group. The minimum age in PUVA, NBUVB and PUVASOL is 19, 17, 25 years respectively. The maximum age in PUVA, NBUVB and PUVASOL is 61, 63, 58 years respectively.

Table -1

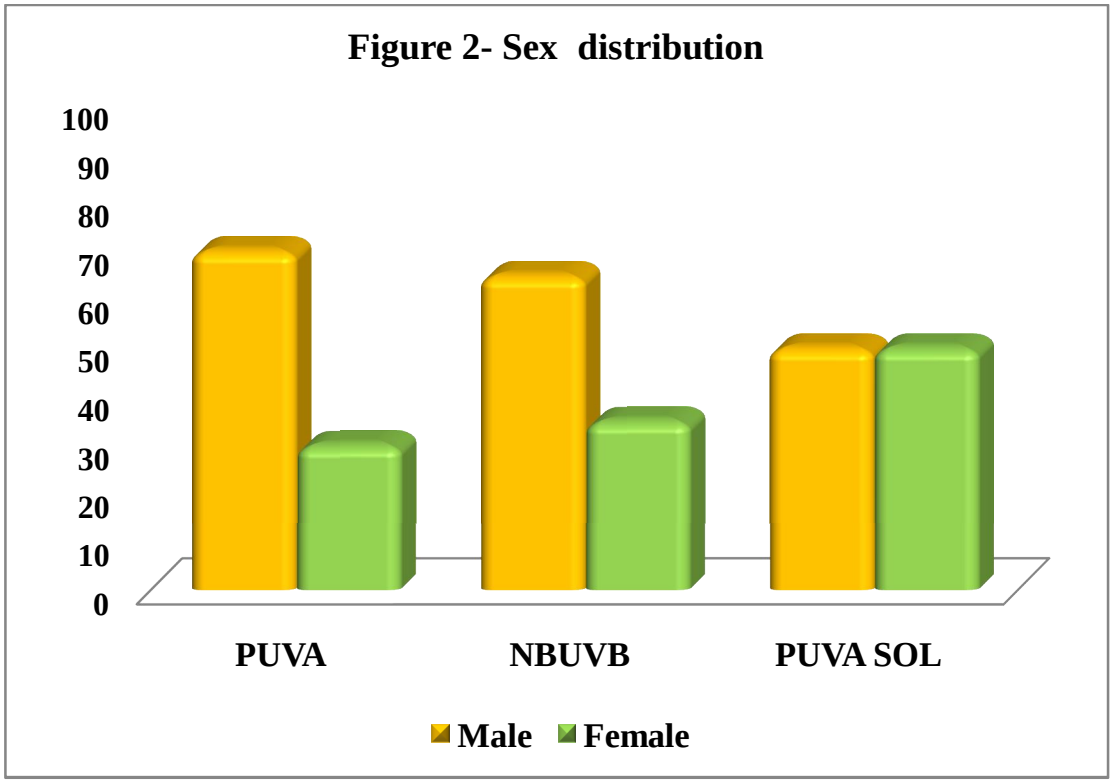
Showing age distribution

Age	N	Mean	Std. Dev	Median	Minimum	Maximum
PUVA	20	38.05	12.05	37.00	19	61
NBUVB	20	38.05	14.30	36.50	17	63
PUVA SOL	20	39.45	8.77	37.50	25	58



SEX DISTRIBUTION

Males were more in our study when compared to females.



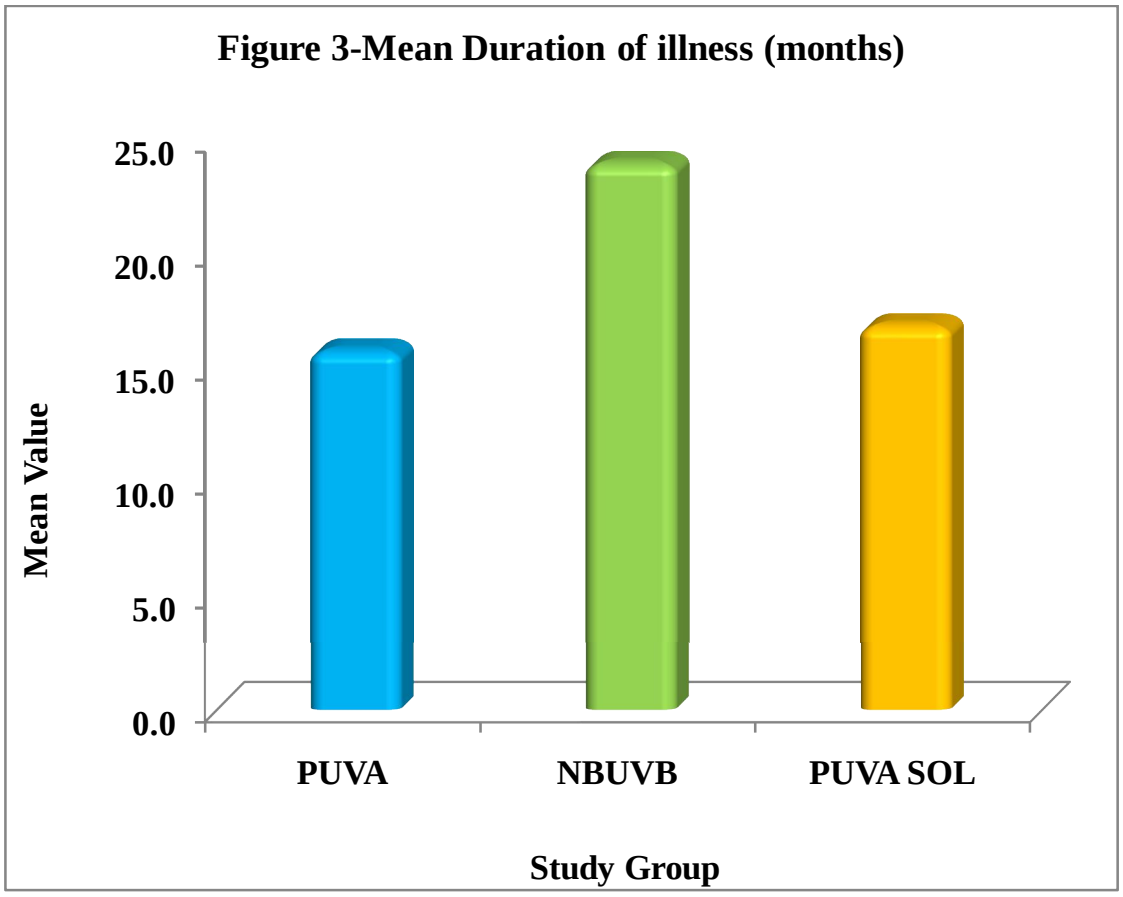
In PUVA group 70 % were males, 30 % were females. In NBUVB group 65 % were males, 35% were females and PUVASOL group 50 % were males, 50 % were females.

Table 2- showing Sex distribution

Groups	Sex distribution (%)	
	Male	**Female**
PUVA	70	30
PUVASOL	65	35
NBUVB	50	50

DURATION OF ILLNESS

The duration of illness varies in three groups. In PUVA group Duration of illness varies from 2 months and 4 years. In NBUVB group duration varies from 1month to 8 years. In PUVASOL group duration of illness varies from 2 months to 8 years.



The mean duration in PUVA group is 15.78 months, NBUVB group is 26.70 months, and PUVASOL group is 20 months.

Table 3

Showing duration of illness in three groups

Duration (months)	N	Mean	Std. Dev	Median	Minimum	Maximum
PUVA	20	15.78	14.21	12.00	2	48
NBUVB	20	24.00	26.70	10.50	1	96
PUVA SOL	20	16.90	20.76	9.00	2	96

FAMILY HISTORY

Family history was present in 15% of patients in all three groups in our study.

SCALP INVOLVEMENT

Scalp involvement were present in 19 of our patients. 6 patients in PUVA group, 8 patients in NBUVB group and 5 patients in PUVASOL group.

Table 4

Showing percentage of scalp involvement

Group	Scalp involvement	
	Number of patients	Percentage (%)
PUVA	6	30
NBUVB	8	40
PUVASOL	5	25

NAIL CHANGES

Nail changes were present in 21 of our patients, 7 in each group.

The Commonly noted nail changes were pitting , subungual hyperkeratosis, ridging. More than one morphological nail changes were present in a single patient.

In PUVA group

7 had pitting,

2 had subungual hyperkeratosis,

1 had ridging.

In NBUVB group

7 had pitting,

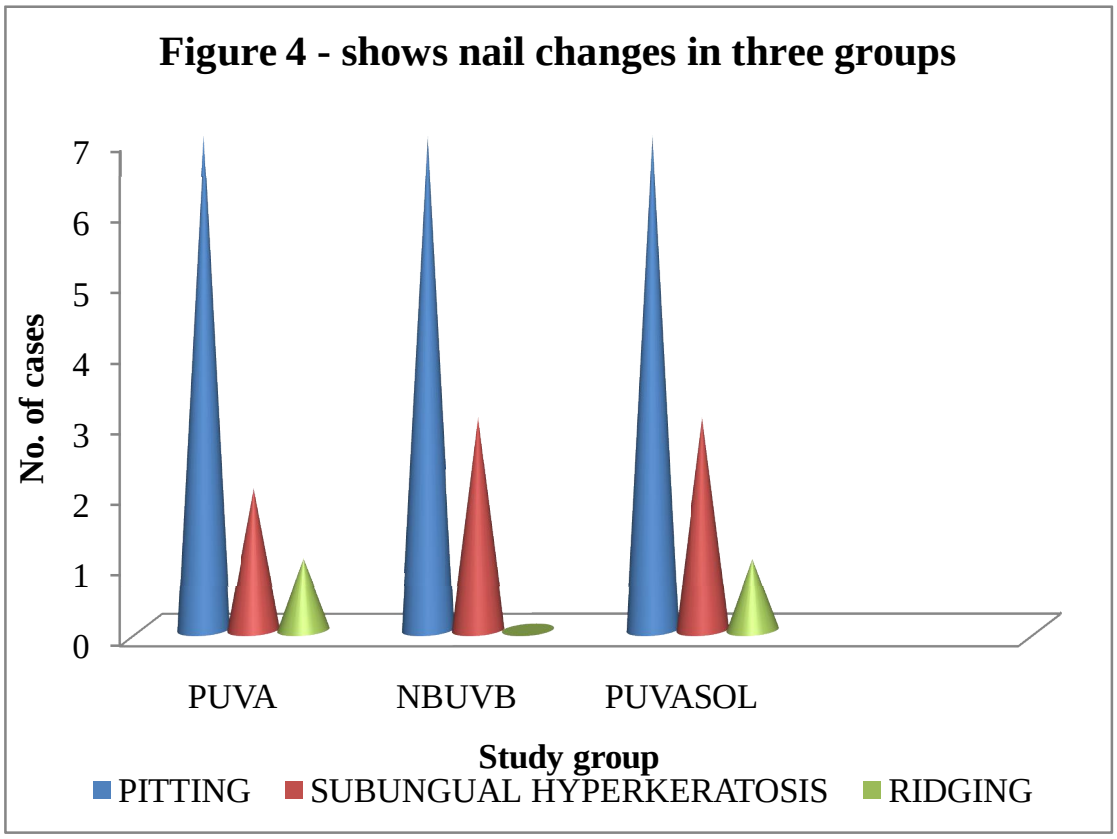
3 had subungual hyperkeratosis.

In PUVASOL group

7 had pitting,

3 had subungual hyperkeratosis,

1 had ridging.



Pitting was the most common type of nail involvement in all three groups of our study.

MUCOUS MEMBRANE

There was no mucous membrane involvement in our patients.

JOINT INVOLVEMENT

Joint involvement was present in 9 of our patients. 2 of them in PUVA group (10%), 3 of them in NBUVB group (15%), 4 of them in PUVASOL group (20%) had joint involvement.

Table 5

Showing joint involvement among three groups

Group	Number of patients	Percentage (%)
PUVA	3	10
NBUVB	3	15
PUVASOL	4	20

Figure 5 shows percentage of scalp, nail, and joint involvement in PUVA, NBUVB and PUVASOL group.

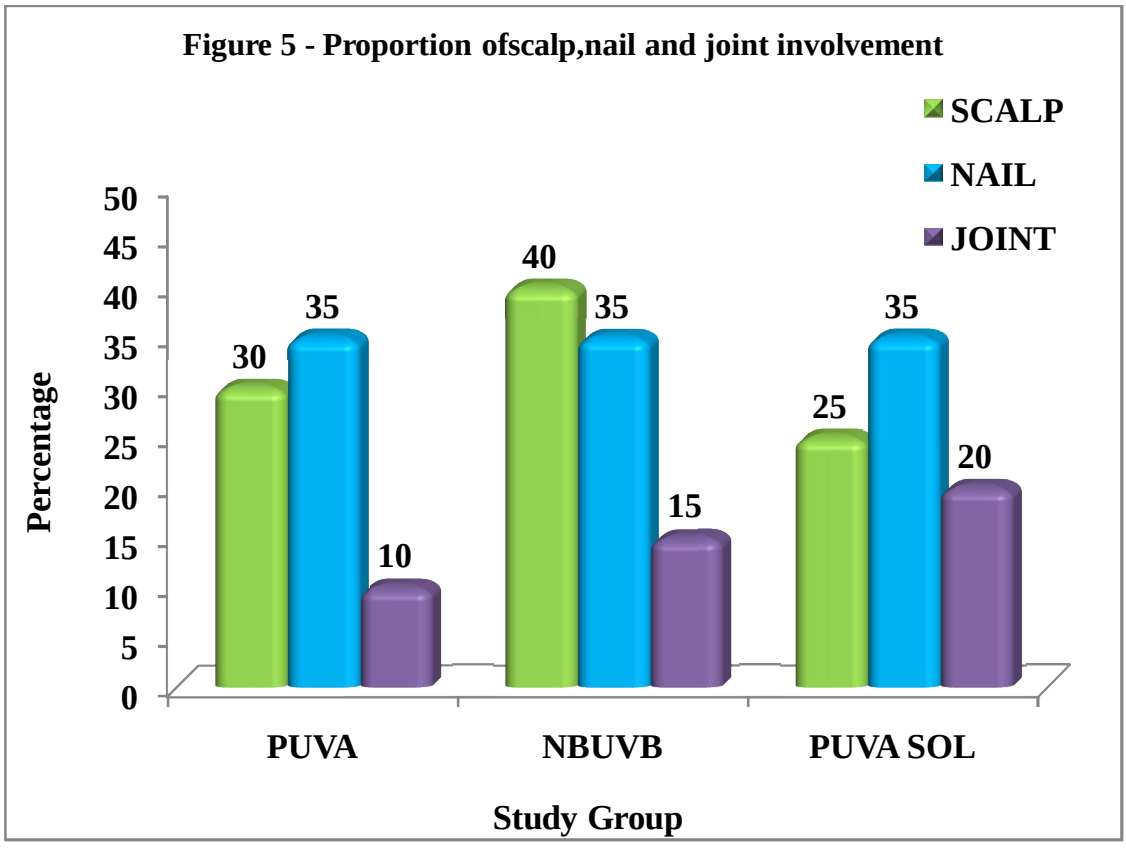


Table 6

Chi-Square test to compare the proportions of scalp, nail and joint involvement between the three groups

Variables		Group						Total		P-Value
		PUVA		NBUVB		PUVA SOL				
		N	%	N	%	N	%	N	%	
SCALP	No	14	70.0	12	60.0	15	75.0	41	68.3	0.583
	Yes	6	30.0	8	40.0	5	25.0	19	31.7	
NAIL	No	13	65.0	13	65.0	13	65.0	39	65.0	0.999
	Yes	7	35.0	7	35.0	7	35.0	21	35.0	
JOINT	No	18	90.0	17	85.0	16	80.0	51	85.0	0.900*
	Yes	2	10.0	3	15.0	4	20.0	9	15.0	
Total		20	100.0	20	100.0	20	100.0	60	100.0	

* Fisher's exact test p-value

PASI REDUCTION

The following tables shows the mean PASI score at baseline and reduction of mean PASI score at 4 weeks, 8 weeks, 12 weeks, 16 weeks in PUVA, NBUVB, PUVASOL groups.

The mean PASI score at baseline (Table 7) was 32.20 in PUVA group, 31.04 in NBUVB group, and 34.59 in PUVASOL group. The minimum mean PASI score at baseline in PUVA, NBUVB and PUVASOL group is 18.0, 15.2 and 18.9 respectively. The maximum mean

PASI score at baseline in PUVA, NBUVB and PUVASOL group is 44.0, 47.8 and 44.0 respectively.

Table 7

Showing mean PASI score at baseline in three groups

PASI 0	N	Mean	Std. Dev	Median	Minimum	Maximum
PUVA	20	32.20	7.59	32.40	18.0	44.0
NBUVB	20	31.04	9.02	31.35	15.2	47.8
PUVA SOL	20	31.59	8.04	33.00	18.9	44.0

The mean PASI score at 4 weeks (Table 8) was 20.76 in PUVA group, 20.82 in NBUVB group, and 24.96 in PUVASOL group.

The minimum mean PASI score at 4 weeks in PUVA, NBUVB and PUVASOL group is 9.4, 10.1, and 12.4 respectively. The maximum mean PASI score at 4 weeks in PUVA, NBUVB and PUVASOL group is 32.6, 35.6 and 42.6 respectively.

Table 8

showing mean PASI score at 4 weeks in three groups

PASI 4	N	Mean	Std. Dev	Median	Minimum	Maximum
PUVA	20	20.76	6.48	20.35	9.4	32.6
NBUVB	19	20.82	7.95	20.80	10.1	35.6
PUVA SOL	19	24.96	7.92	24.60	12.4	42.6

The mean PASI score at 8 weeks (Table 9) was 10.54 in PUVA group, 11.98 in NBUVB group, and 17.71 in PUVASOL group.

The minimum mean PASI score at 8 weeks in PUVA, NBUVB and PUVASOL group is 1.2, 1.5 and 6.2 respectively. The maximum mean PASI score at 8 weeks in PUVA, NBUVB and PUVASOL group is 21.4, 26.4 and 38.4 respectively.

Table 9

Showing mean PASI score at 8 weeks in three groups

PASI 8	N	Mean	Std. Dev	Median	Minimum	Maximum
PUVA	18	10.54	4.95	9.85	1.2	21.4
NBUVB	19	11.98	7.10	10.80	1.5	26.4
PUVA SOL	18	17.71	50.71	15.40	6.2	38.4

The mean PASI score at 12 weeks (Table 10) was 3.18 in PUVA group, 5.92 in NBUVB group, and 12.47 in PUVASOL group.

The minimum mean PASI score at 12 weeks in PUVA, NBUVB and PUVASOL group is 0.0, 0.0 and 2.1 respectively. The maximum mean PASI score at 12 weeks in PUVA, NBUVB and PUVASOL group is 10.5, 20.8 and 36.7 respectively.

Table 10

Showing mean PASI score at 12 weeks in three groups

PASI 12	N	Mean	Std. Dev	Median	Minimum	Maximum
PUVA	18	3.18	3.30	2.15	0.0	10.5
NBUVB	19	5.92	5.61	4.60	0.0	20.8
PUVA SOL	18	12.47	4.64	9.90	2.1	36.7

The mean PASI score at 16 weeks (Table 11) was 0.38 in PUVA group, 0.83 in NBUVB group, and 7.76 in PUVASOL group. The minimum mean PASI score at 16 weeks is 0.0 in all three groups. The maximum mean PASI score at 16 weeks in PUVA, NBUVB and PUVASOL group is 2.7, 4.6 and 32.4 respectively.

Table 11

Showing mean PASI score at 16 weeks in three groups

PASI 16	N	Mean	Std. Dev	Median	Minimum	Maximum
PUVA	18	0.38	0.81	0.00	0.0	2.7
NBUVB	17	0.83	1.51	0.00	0.0	4.6
PUVA SOL	18	7.76	3.20	3.60	0.0	32.4

From tables 7- 11 we inferred that there was gradual reduction in PASI score in all three groups.

Table 12

Shows mean reduction in PASI score among three groups

Duration	Mean PASI score		
	PUVA	NBUVB	PUVASOL
Baseline	32.20	31.04	31.59
4 weeks	20.76	20.82	24.96
8weeks	10.54	11.98	17.71
12 weeks	3.18	5.92	12.47
16 weeks	0.38	0.83	7.76

In PUVA group the mean PASI score at baseline is 32.20 and it was reduced to 0.38 at 16 weeks. In NBUVB group the mean PASI score while enrolling in study was 31.04 where as it was reduced to 0.83 at 16 weeks.

In PUVASOL group the mean PASI score was 31.59 at baseline and it was reduced to 7.76 at 16 weeks of PUVASOL therapy.

Therefore the mean reduction of PASI score at 16 weeks is more in PUVA group, followed by NBUVB group. PUVASOL has lesser reduction in mean PASI score among three groups.

Figure 6 - showing mean reduction in PASI scores

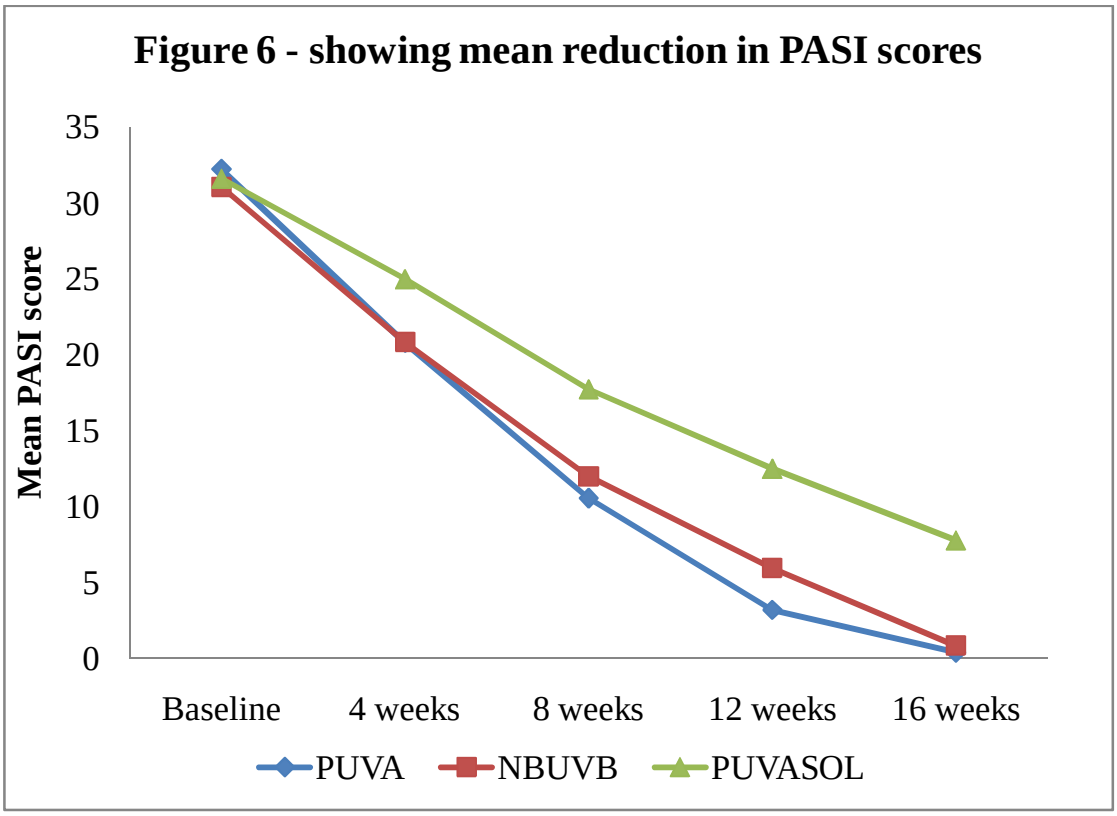


Table 12 shows P values by comparing three groups with one another. There was no statistically significant reduction in PASI score at 0, 4, 8, 12 and 16 weeks when PUVA and NBUVB are compared.

When PUVA and PUVASOL groups are compared there is no statistically difference in reduction in PASI score at 0, 4, 8 weeks. But at

12 and 16 weeks there is statistically significant (P<0.001) reduction in PASI score.

Table 12

Shows P values of PASI Score reduction when two groups are compared

Variables	P-Values		
	PUVA vs NBUVB	**PUVA vs PUVASOL**	**NBUVB vs PUVASOL**
PASI 0	0.579	0.903	0.695
PASI 4	0.933	0.255	0.184
PASI 8	0.627	0.024	0.101
PASI 12	0.150	0.001	0.035
PASI 16	0.694	0.001	0.001

When NBUVB and PUVASOL groups were compared there was no statistically significant difference in PASI score at 0, 4, 8, 12 weeks. However at 16 weeks there is statistically significant PASI reduction (P<0.001).

PERCENTAGE REDUCTION OF PASI SCORE

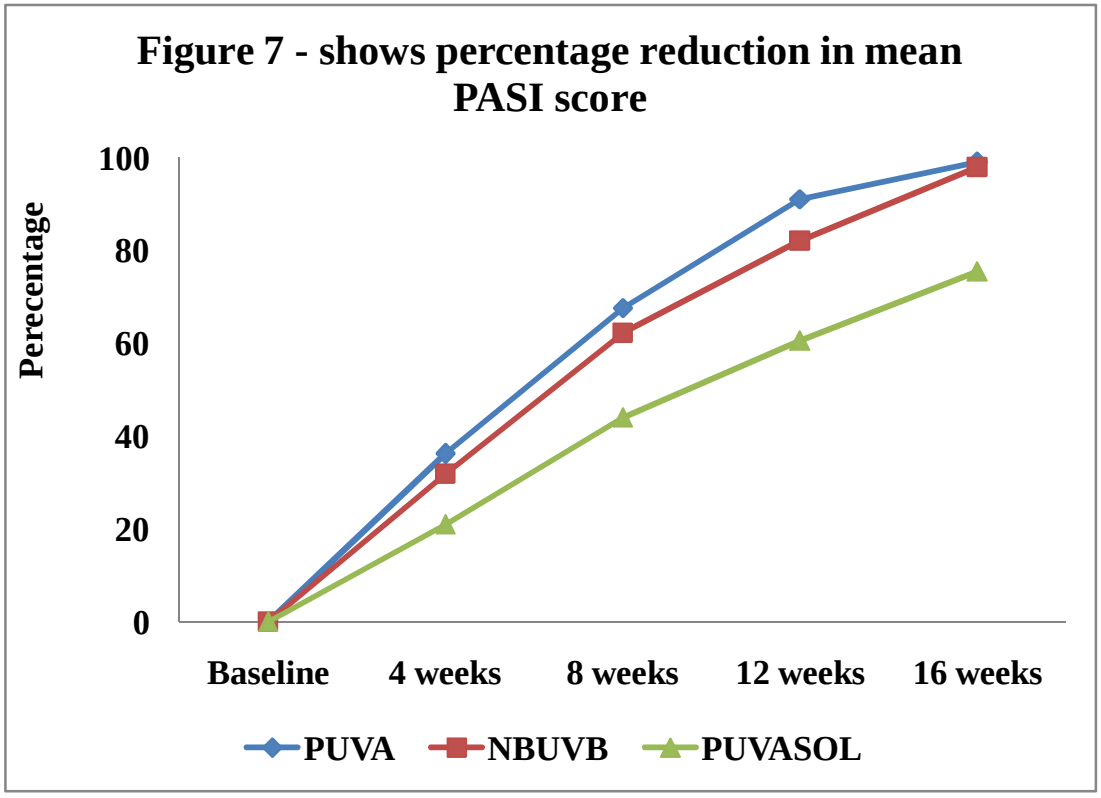
Table – 13

Showing percentage mean reduction in PASI score in three groups

Duration	PUVA	NBUVB	PUVASOL
Baseline	0	0	0
4 weeks	36.2	31.8	20.99
8 weeks	67.5	62.2	43.94
12 weeks	91.0	82.0	60.53
16 Weeks	98.9	97.9	75.44

The above table shows that there is gradual increase in percentage mean reduction of PASI score over weeks. When compared to baseline mean PASI score there was 98.9 % reduction in mean PASI score at 16 weeks in PUVA group and 97.9% reduction in mean PASI score at 16 weeks in NBUVB group. In PUVASOL group there is 75.44% reduction in mean PASI score at 16 weeks.

PUVA group has the maximum percentage reduction in mean PASI score at 16 weeks, closely followed by NBUVB group. PUVASOL has least reduction when all three groups are compared.



DURATION OF TREATMENT

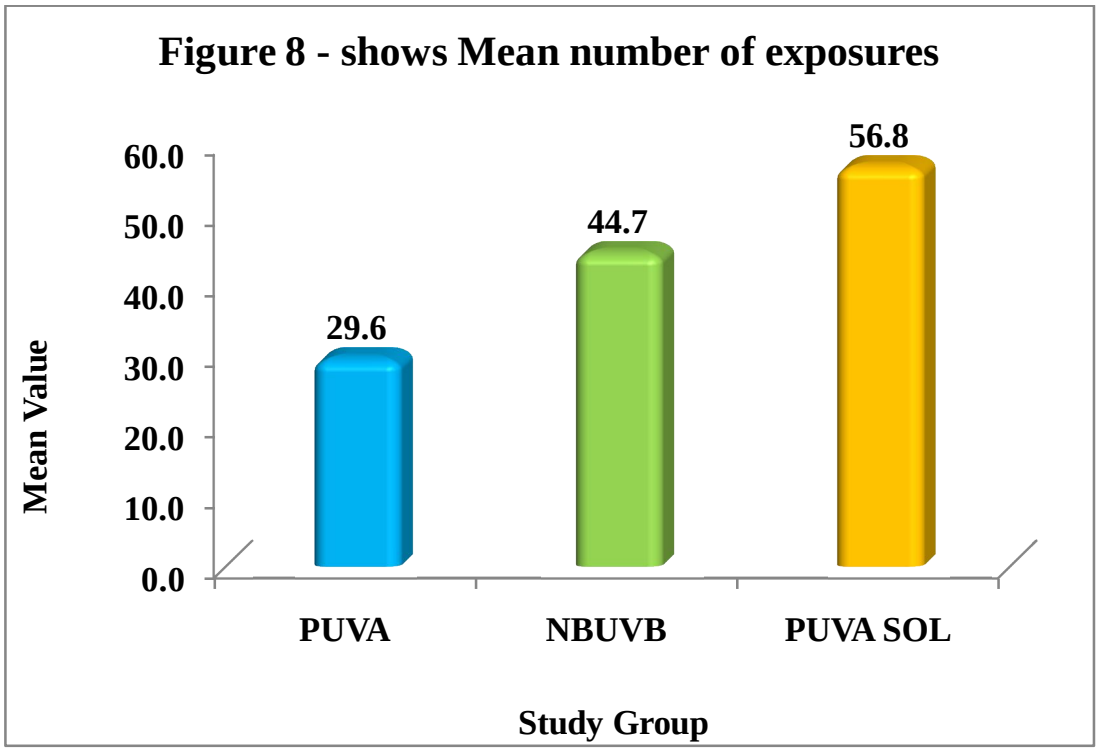
The average number of exposures and total duration of treatment are tabulated below.

Table 14

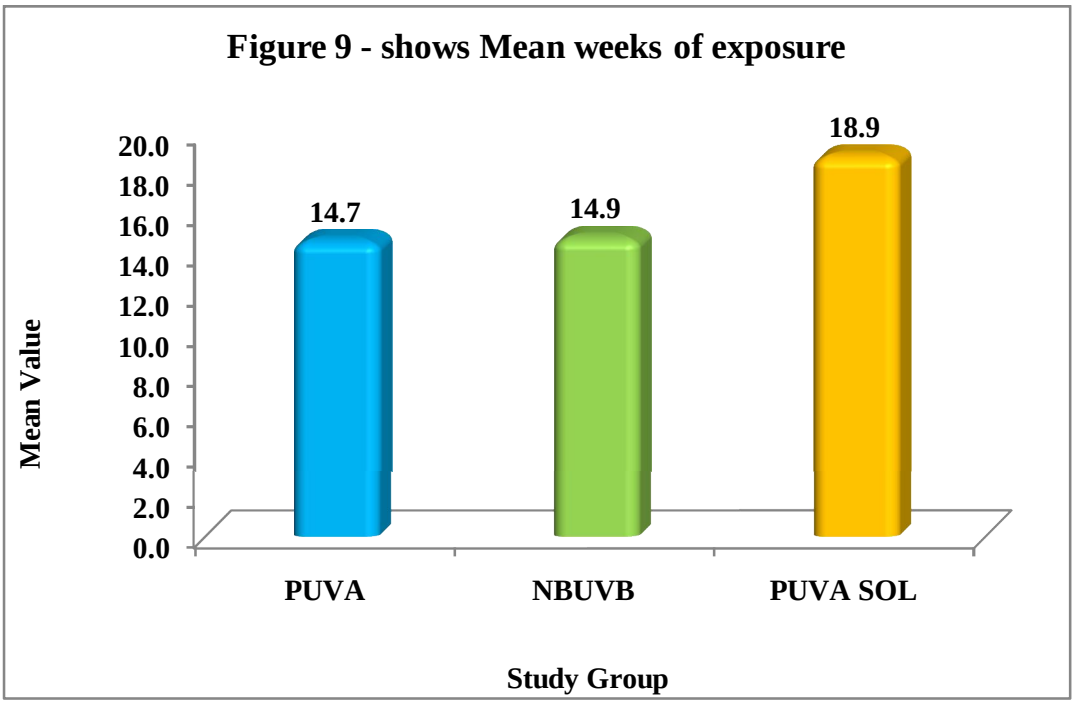
Showing number of weeks of exposure and duration of treatment

Variables	PUVA	NBUVB	PUVASOL
Average number of exposure	29.50	44.65	56.80
Duration of treatment (weeks)	14.72	14.88	18.93

The average number of exposure in PUVA, NBUVB and PUVASOL groups were 29.50, 44.65 and 56.80 respectively.

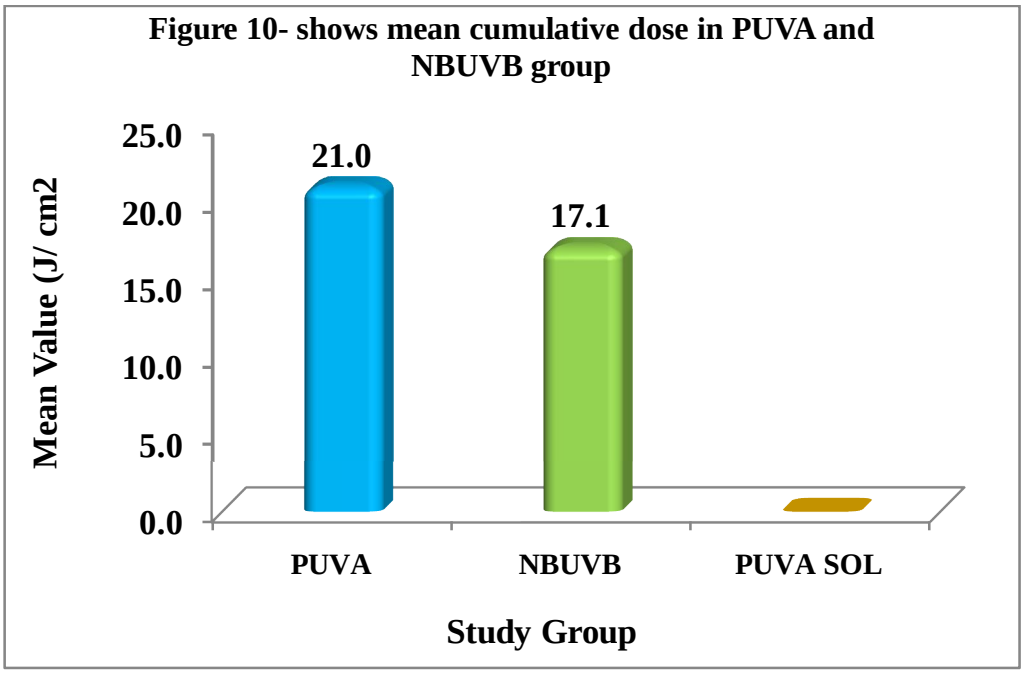


The total duration of treatment in PUVA, NBUVB and PUVASOL groups were 14.72 weeks, 14.88 weeks and 18.93 weeks respectively.



CUMULATIVE DOSE

The cumulative dose of ultraviolet A light for PUVA group is 21.0J/cm^2 and the mean cumulative dose of narrowband ultraviolet B light for NBUVB group is 17.10 J/cm^2 .



RESPONSE TO THERAPY

Based on percentage reduction in PASI score the results were graded as excellent (100%), good (75-100%), moderate (50- 75%) and poor (< 50%).

Response to therapy in PUVA group

In PUVA group out of 20 patients 13 patients had complete clearance at 16 weeks and 5 had good response. 2 patients discontinued treatment at 8 weeks of therapy due to unknown reasons.

Table 14

Response to treatment in PUVA group

Results	No. of patients	Percentage	% reduction in PASI score at 16 weeks
Excellent	13	72.22	100
Good	5	27.78	75-100
Moderate	-	-	50-75
Poor response	-	-	<50
Discontinued	2	10.00	-

Therefore in PUVA group 72.22% of patients had excellent response and 27.78 % of patients had good response at 16 weeks.

Response to therapy in NBUVB group

In NBUVB group out of 20 patients 12 patients had complete clearance at 16 weeks and 5 had good response 1 patients had poor response. 2 patients discontinued treatment at 8 weeks of therapy due to unknown reasons.

Table 15

Response to treatment in NBUVB group

Results	No. of patients	Percentage	% reduction in PASI score at 16 weeks
Excellent	12	60.00	100
Good	5	25.00	75-100
Moderate	-	-	50-75
Poor response	1	5.00	<50
Discontinued	2	10.00	-

Therefore in NBUVB group 60.0% of patients had excellent response and 25.0 % of patients had good response at 16 weeks. 5.0% had poor response

Response to therapy in PUVASOL group

3 patients had complete clearance at 16 weeks and 12 had good response, 3 patients had poor response. 2 patient discontinued therapy due to unknown reasons.

Therefore in PUVASOL group 15 % of patients had excellent response and 60 % of patients had good response at 16 weeks. 15% had poor response

Table 16

Response to treatment in PUVASOL group

Results	No. of patients	Percentage	% reduction in PASI score at 16 weeks
Excellent	3	15.00	100
Good	12	60.00	75-100
Moderate	-	-	50-75
Poor response	3	15.00	<50
Discontinued	2	10.00	-

SIDE EFFECTS

In PUVA group

- 3 patients developed erythema
- 3 patients developed burning sensation
- 2 patients had nausea
- 1 patient had pruritis

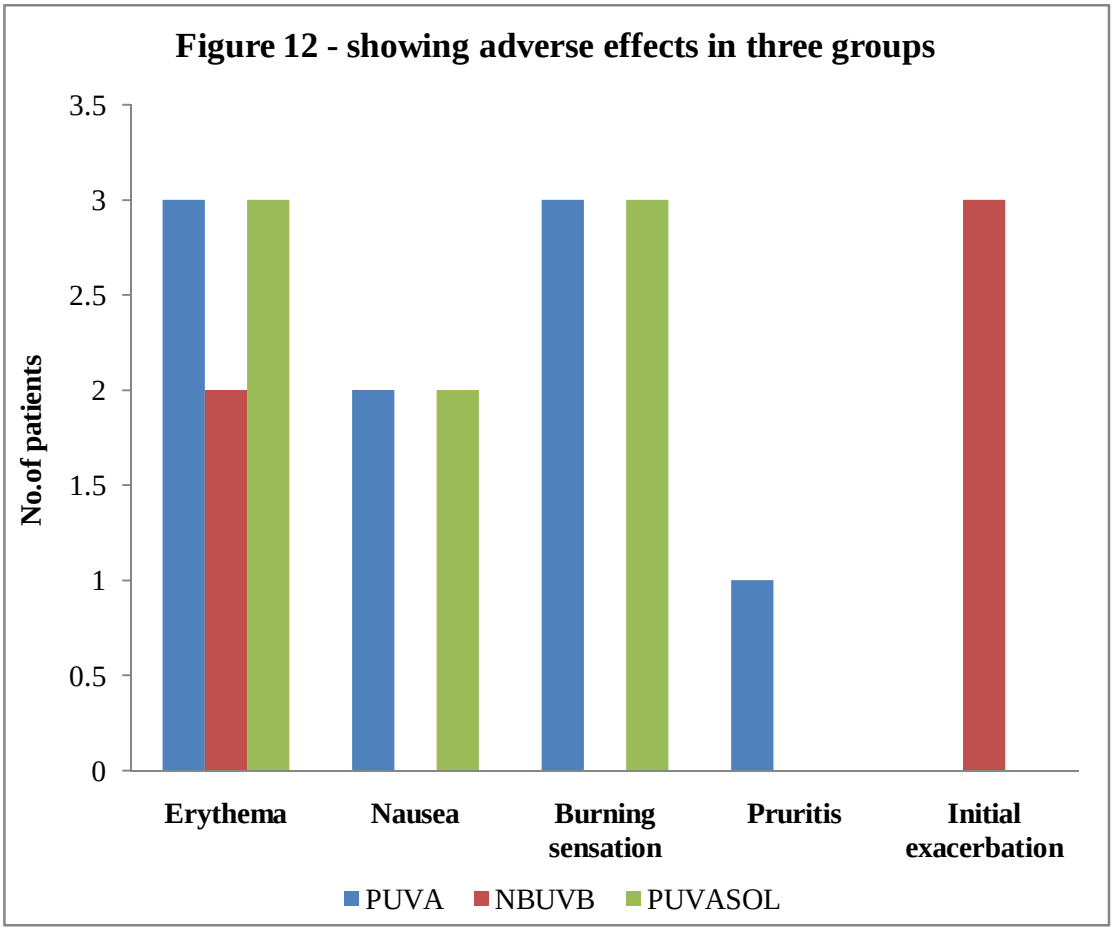
In NBUVB group

- 3 patients developed erythema
- 3 patients developed initial exacerbation

In PUVASOL group

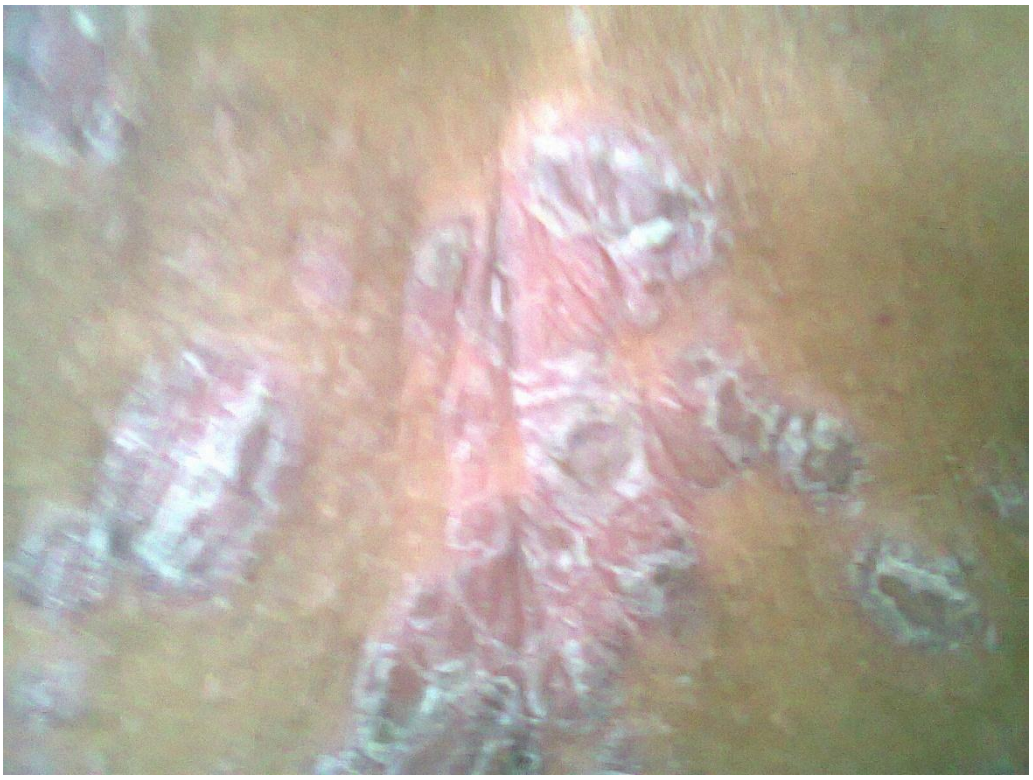
- 3 patients developed erythema
- 3 patients developed nausea

Figure 12 - showing adverse effects in three groups

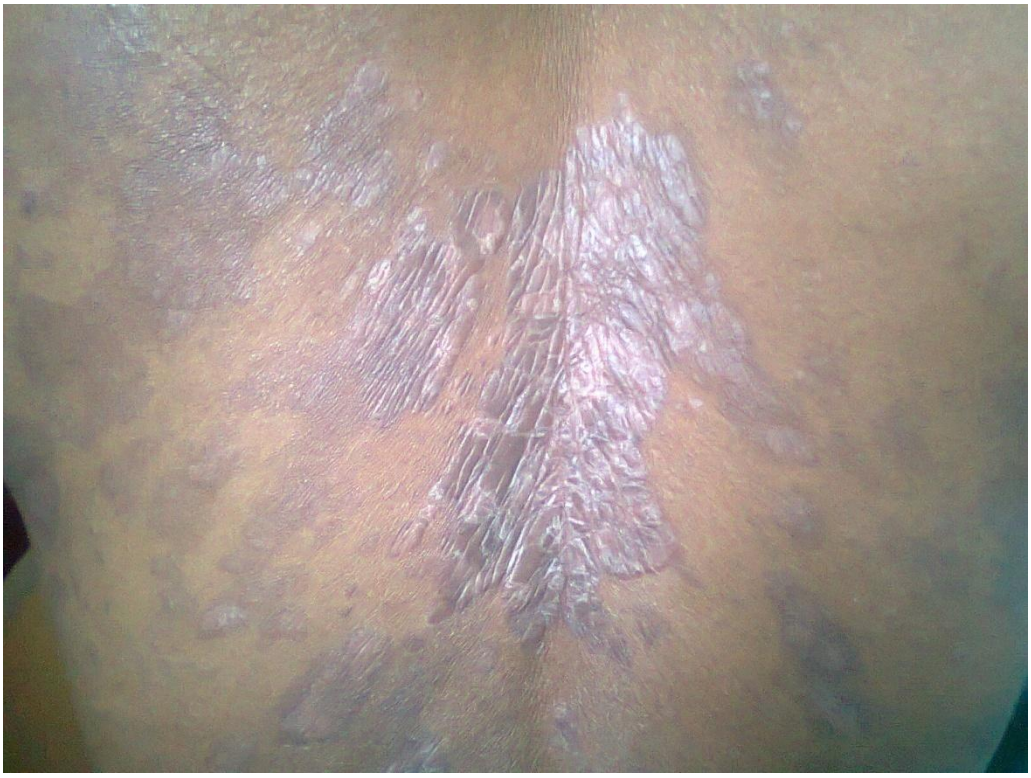


PUVA THERAPY

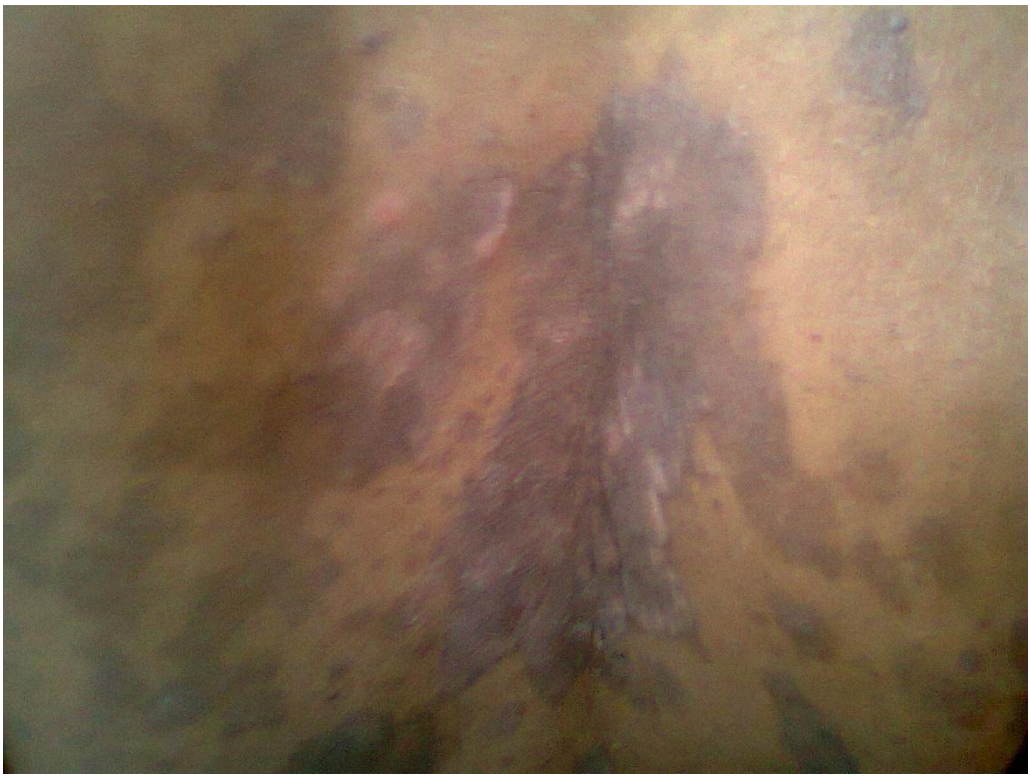
BEFORE TREATMENT



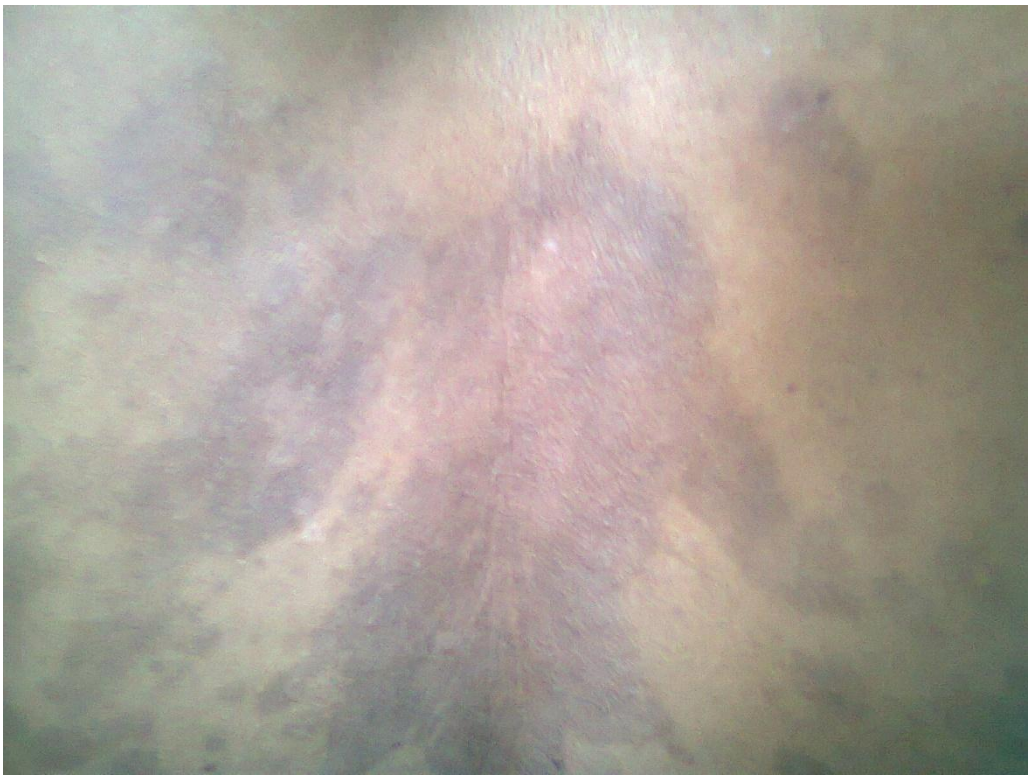
SAME PATIENT AFTER 4 WEEKS OF TREATMENT



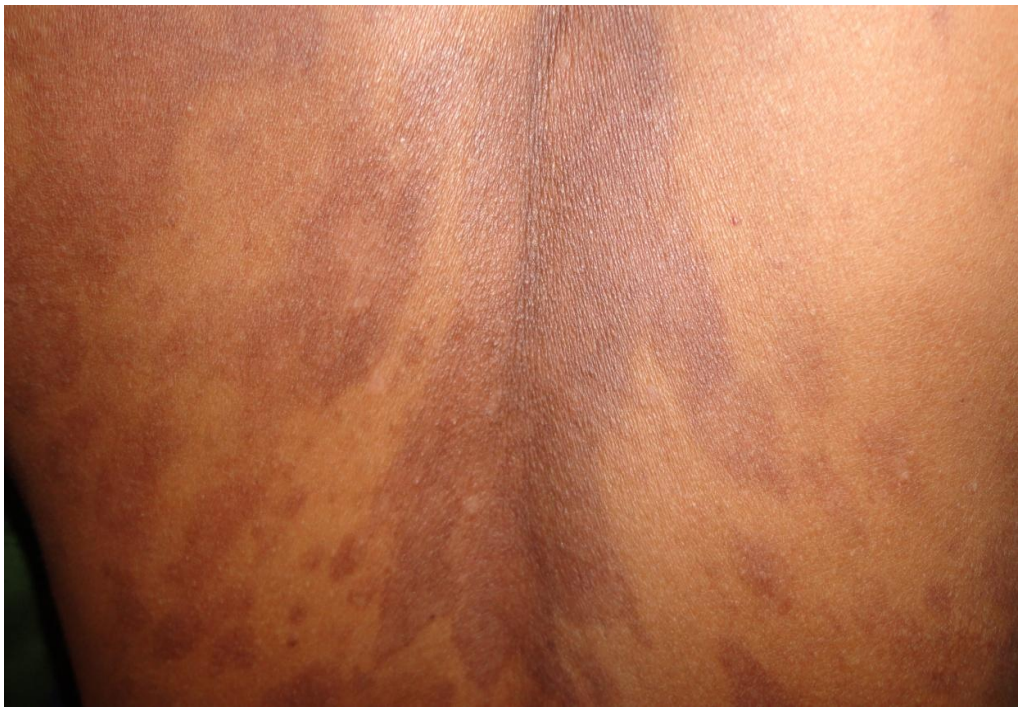
SAME PATIENT AFTER 8 WEEKS OF TREATMENT



SAME PATIENT AFTER 12 WEEKS OF TREATMENT



SAME PATIENT AFTER 16 WEEKS OF TREATMENT



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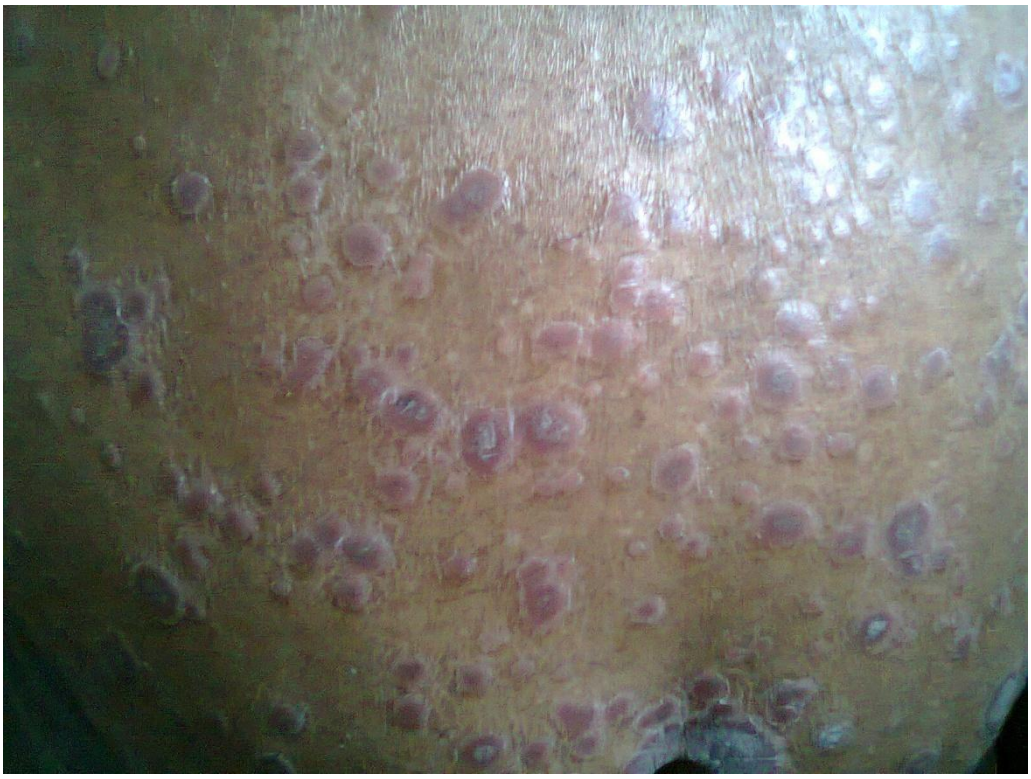

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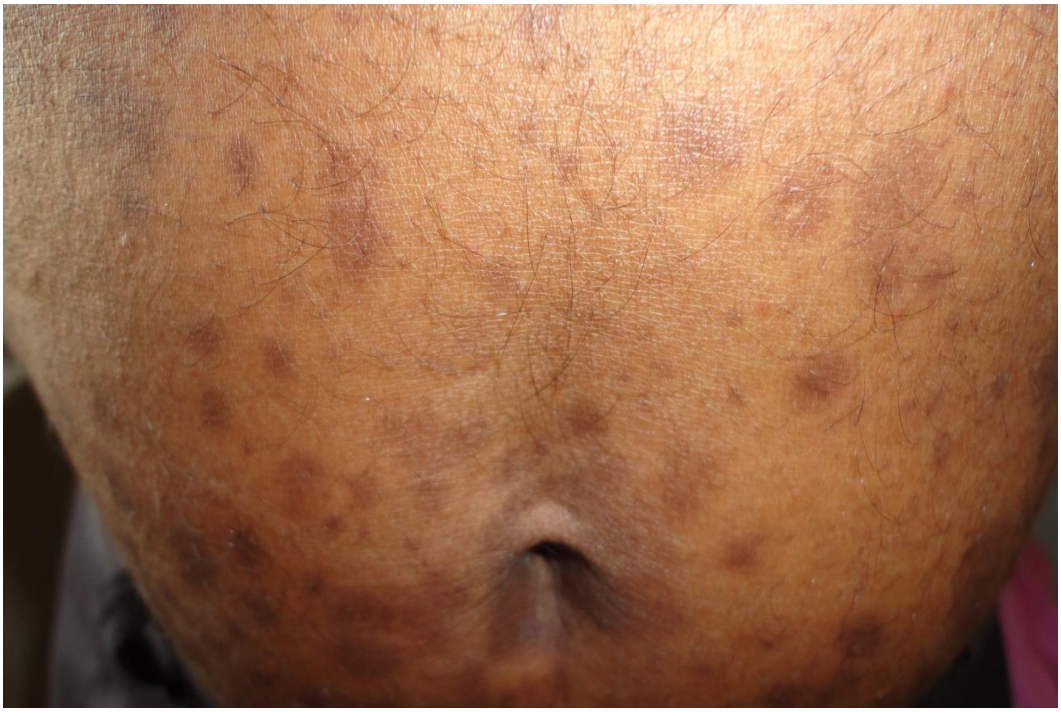
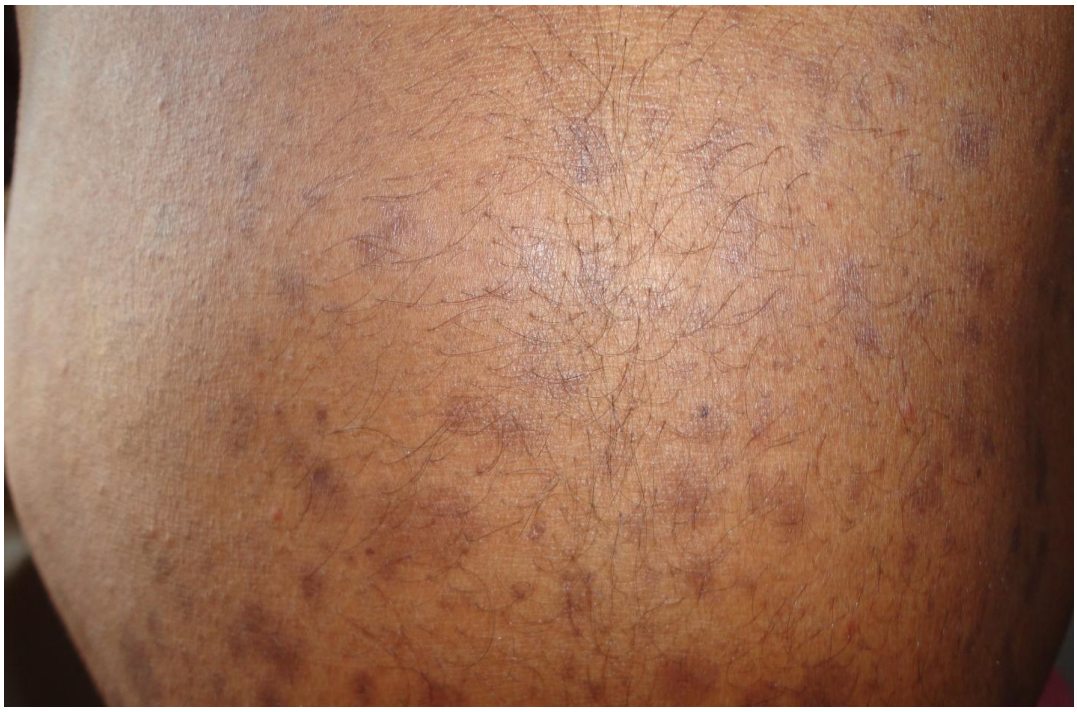
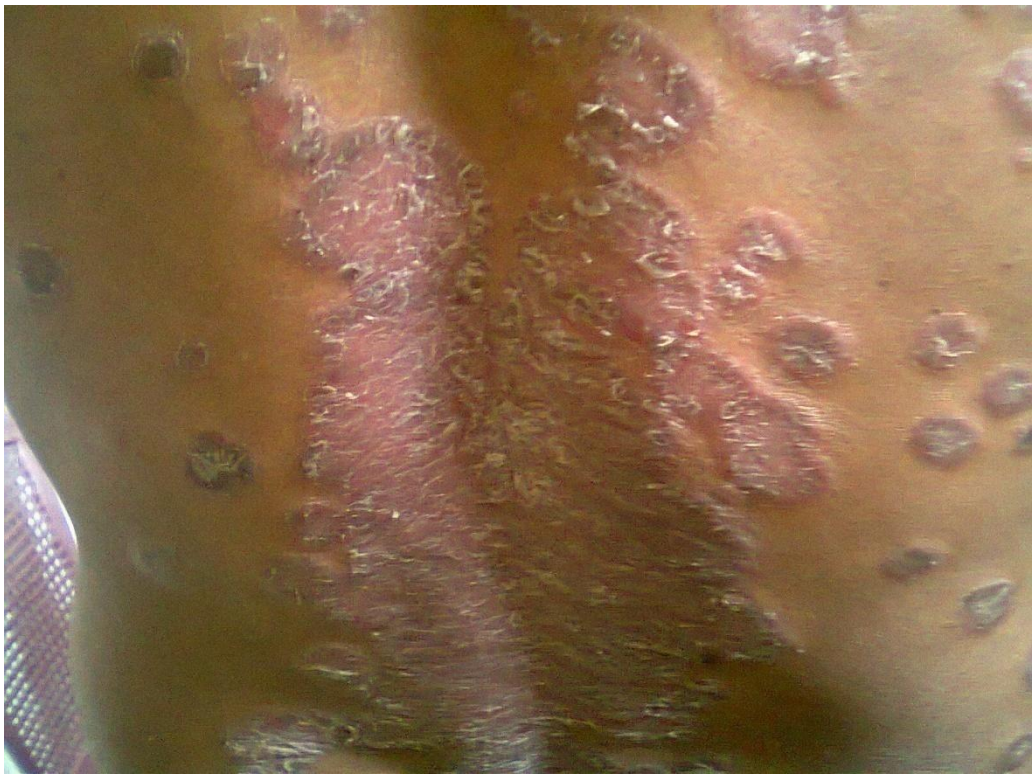


SAME PATIENT AFTER 16 WEEKS OF TREATMENT

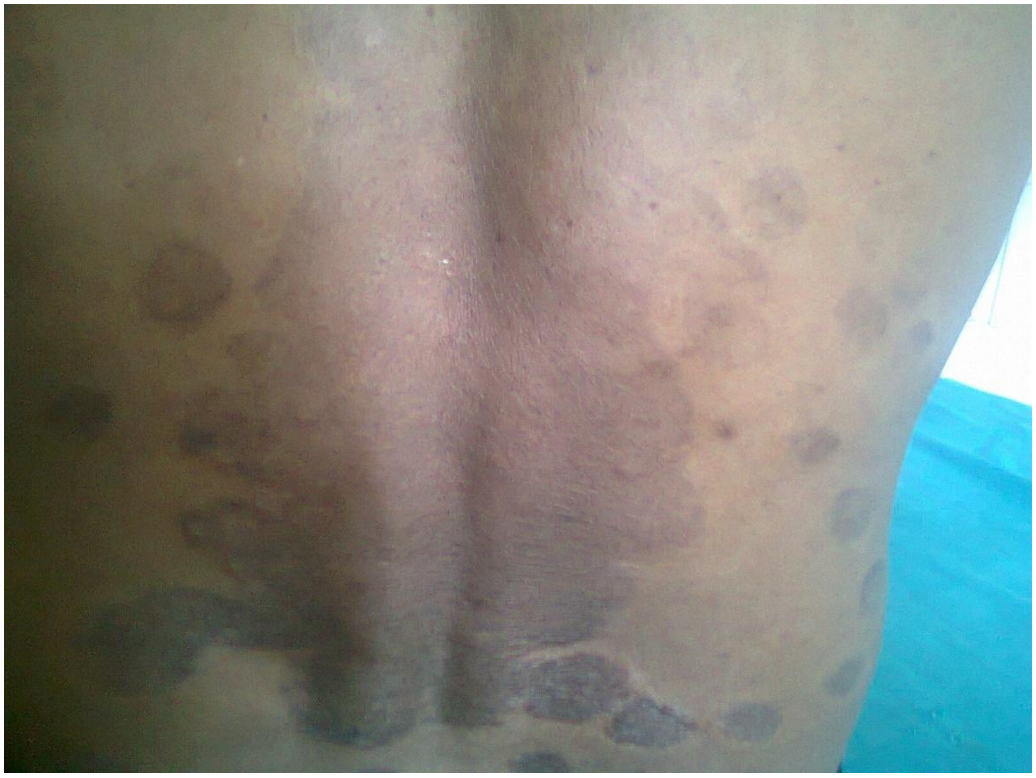


NBUVB THERAPY

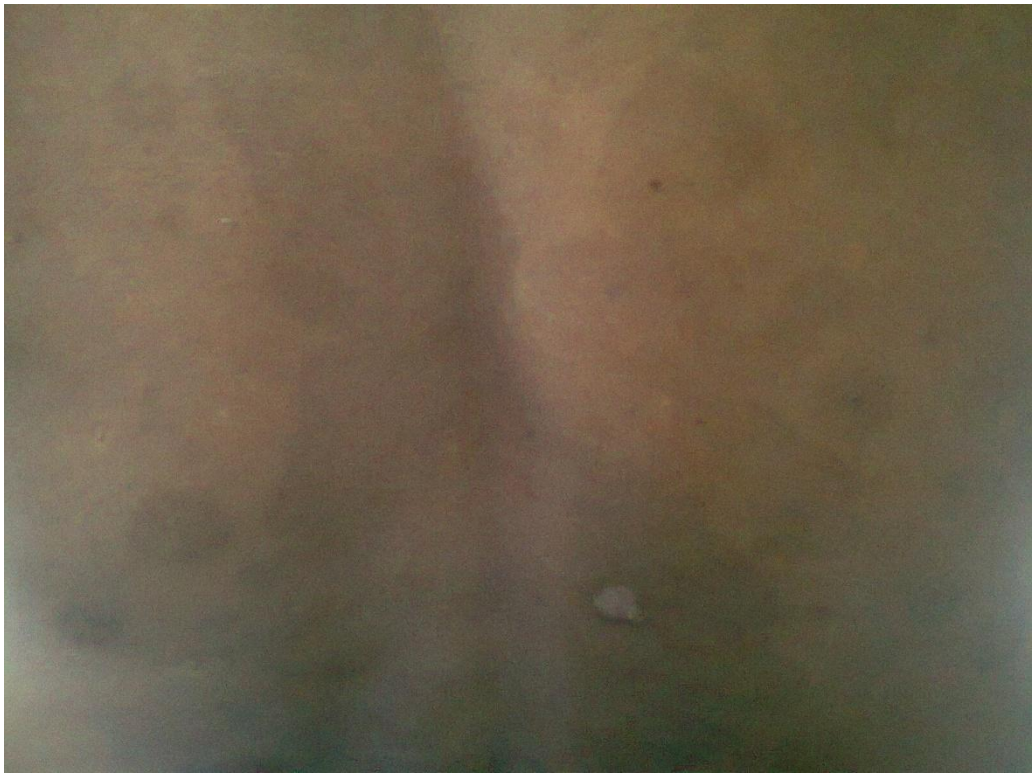
BEFORE TREATMENT



SAME PATIENT AFTER 8 WEEKS OF TREATMENT



SAME PATIENT AFTER 16 WEEKS OF TREATMENT



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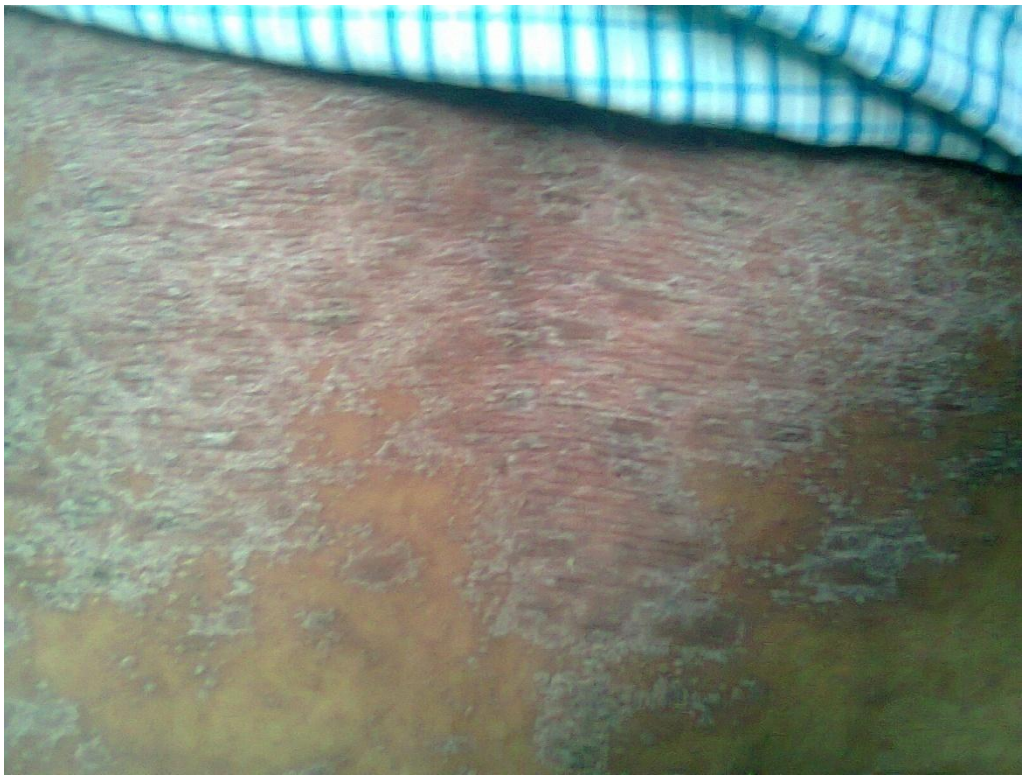
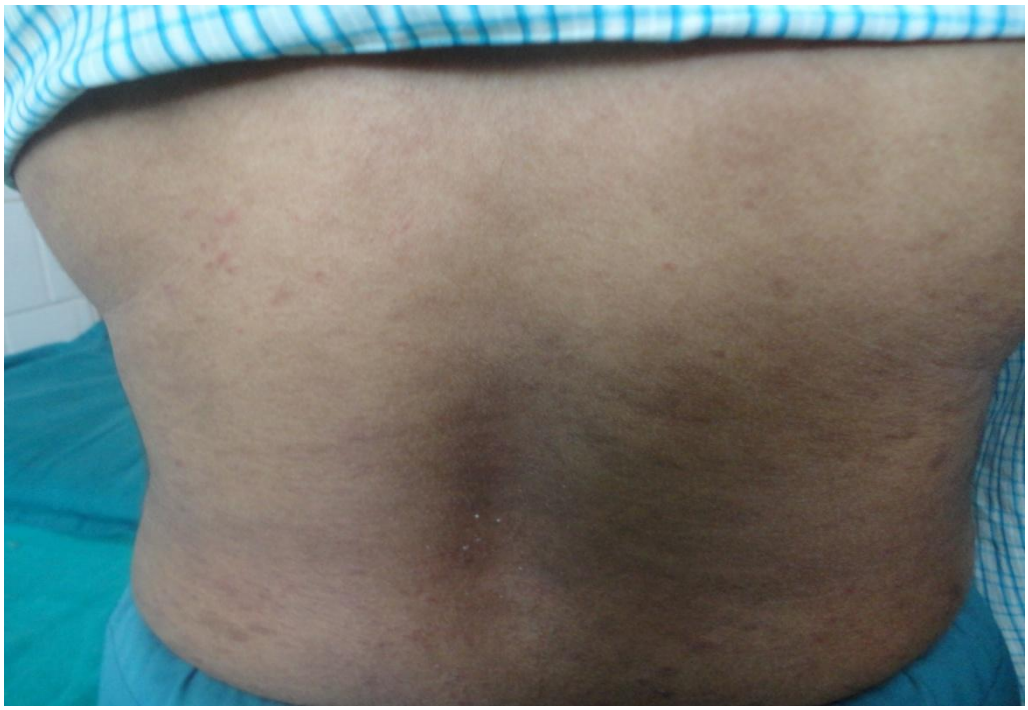
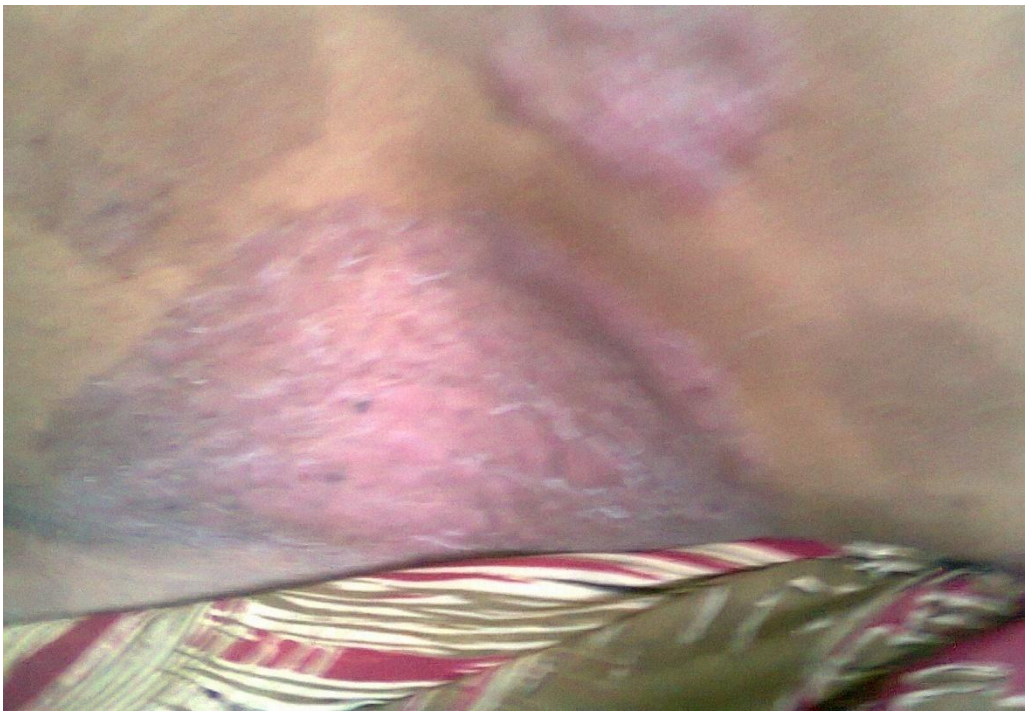


AFTER 12 WEEKS OF TRAETMENT

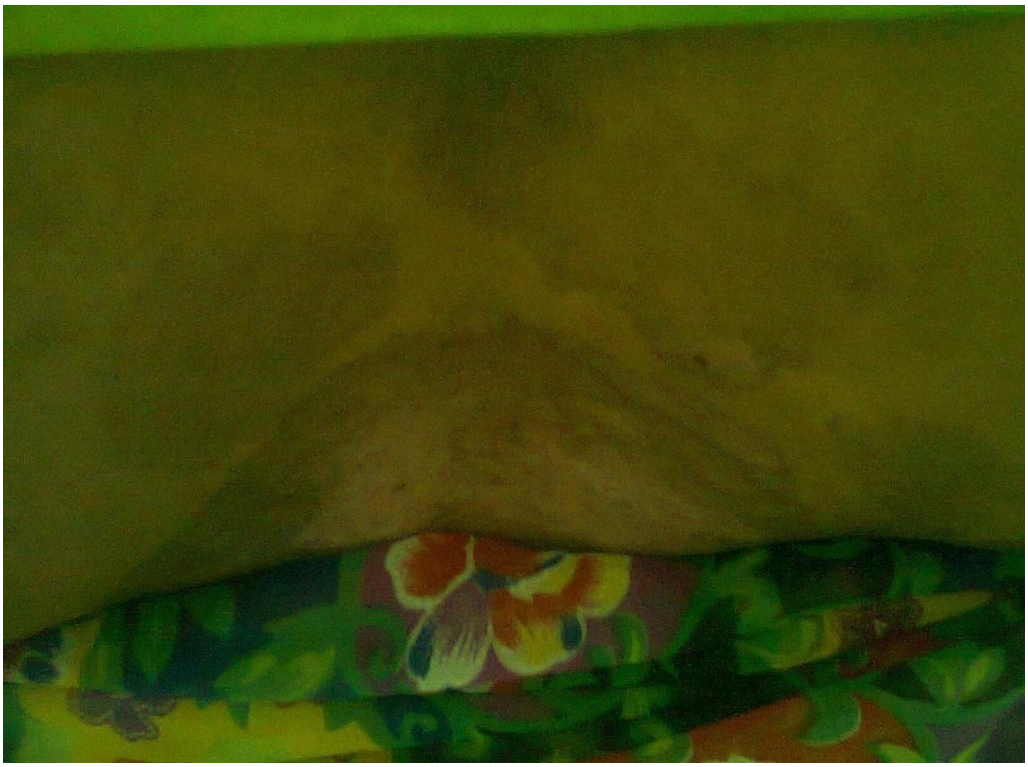


PUVASOL THERAPY

BEFORE TREATMENT



SAME PATIENT AFTER 12 WEEKS OF TREATMENT



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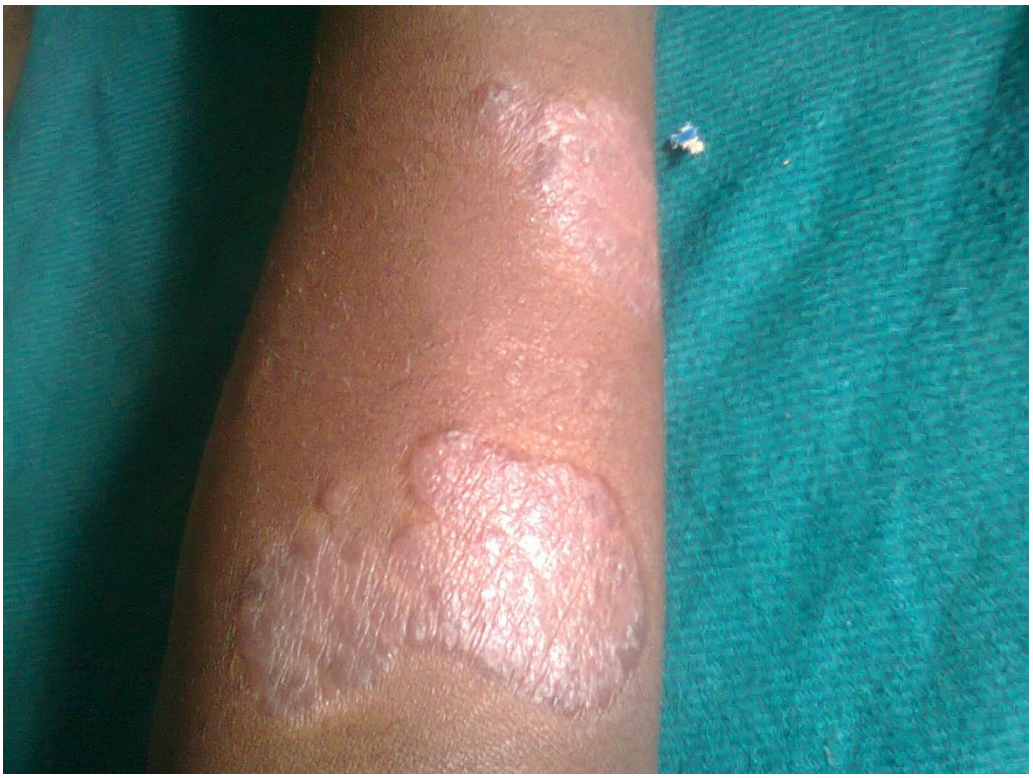
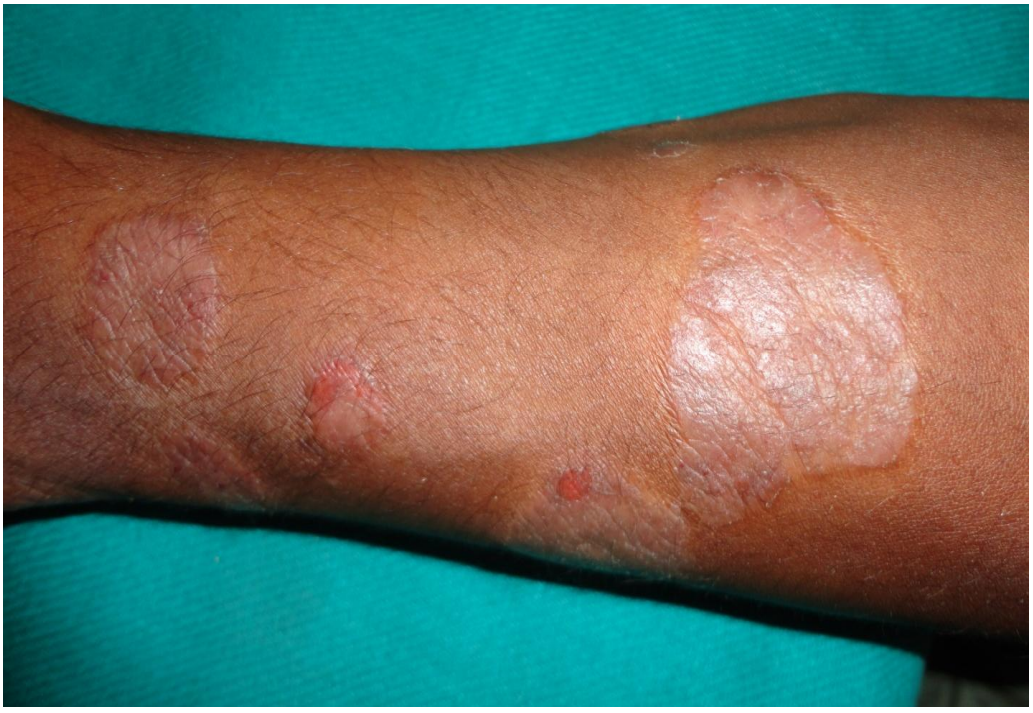
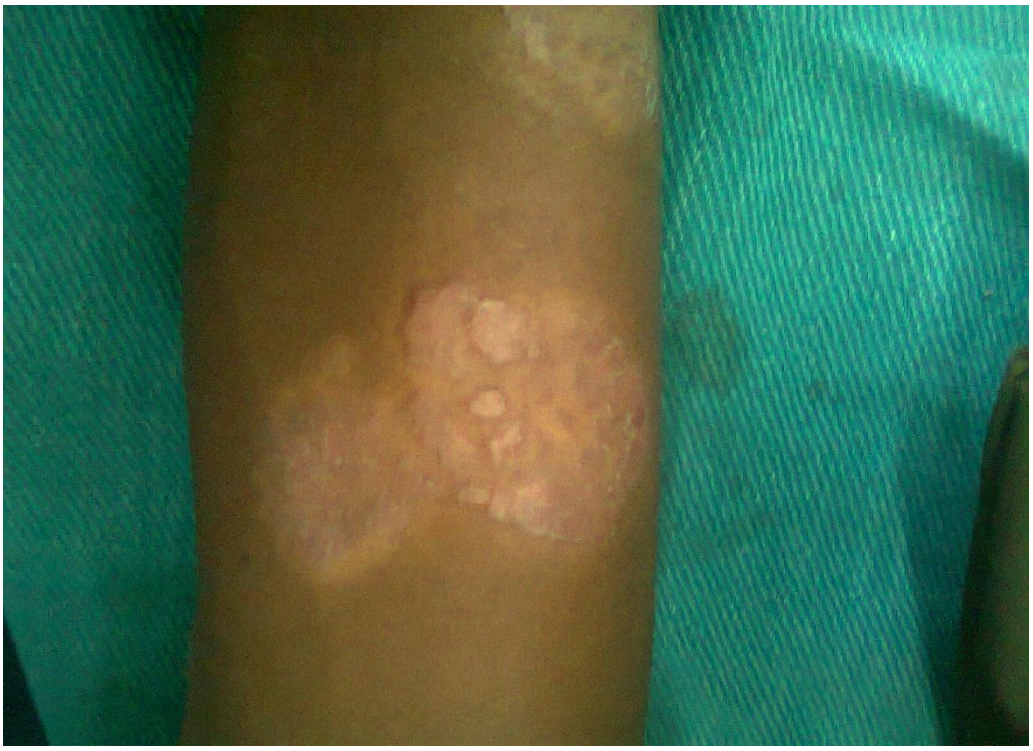


AFTER 8 WEEKS OF TREATMENT



AFTER 12 WEEKS OF TREATMENT



PHOTOTHERAPY UNIT

DISCUSSION

Psoralen ultraviolet A therapy, Narrow band ultraviolet B therapy and PUVASOL are the standard therapeutic regimens available for the management of psoriasis.

There are few studies which compares the therapeutic efficacy of PUVA and NBUVB in treatment of psoriasis. No studies have compared the efficacy of PUVSOL with PUVA and NBUVB.

So the present study compares the therapeutic efficacy of PUVA, NBUVB and PUVASOL in the management of psoriasis.

We enrolled 60 patients with chronic plaque type psoriasis involving more than 20% body surface area for the study. They were randomly divided into three groups.

All three groups were well matched in terms of age, duration of lesions and baseline PASI score. They were followed up weekly after initiating treatment. PASI score were calculated at 0, 4, 8, 12 and 16 weeks.

COMPARISION OF PUVA WITH NBUVB GROUP

In PUVA group the mean baseline PASI score is 32.20 and mean PASI score at 16 weeks is 0.38. Therefore there is 98.9% reduction in PASI score at end of 16 weeks. In NBUVB group the mean baseline PASI score is 31.04 and at mean PASI score at 16 weeks is 0.83. Therefore there is 97.9% reduction in PASI score at end of 16 weeks. From above data it is inferred that both groups showed good clearance of lesions after 16 weeks. The p value is 0.694 which is not statiscally significant.

However the mean cumulative dose for NBUVB (17.10 J/cm^2) is less than the mean cumulative dose for PUVA (21.00 J/cm^2).

So both PUVA and NBUVB therapy produces clearance of lesions with equal efficacy, however the mean cumulative dose is lower for NBUVB. This observation in our study is similar to the study conducted by Gordon et al[81] who did a randomized control study in 100 patients with plaque type psoriasis. An Indian study conducted by Dayal S et al[82] from Haryana also shows similar results.

The mean number of exposure in PUVA group is 14.72 weeks and 14.88 weeks in NBUVB group which is more or less equal. Markham et

al[83] in his study showed that the mean number of exposure is lower in PUVA group than that of NBUVB group.

Koo et al[84] reported that tazarotene plus NBUVB phototherapy is significantly more effective than NBUVB phototherapy alone for treatment of psoriasis.

COMPARISION OF PUVA WITH PUVASOL GROUP

In PUVA group the mean baseline PASI score is 32.20 and mean PASI score at 16 weeks is 0.38. Therefore there is 98.9% reduction in PASI score at end of 16 weeks. In PUVASOL group the mean baseline PASI score is 31.59 and mean PASI score at 16 weeks is 7.76. Therefore there is 75.44% reduction in PASI score at end of 16 weeks. From above data it is inferred that PUVA group showed better clearance of lesions after 16 weeks when compared to PUVASOL group. The p value < 0.005 this is statistically significant.

So PUVA therapy produces clearance of lesions with greater efficacy when compared to PUVASOL.

The mean number of exposure in PUVA group is 14.72 weeks and 18.97 weeks in PUVASOL group which again shows PUVA therapy clears the lesion early when compared to PUVASOL therapy.

In our study 15% of patients in PUVASOL showed complete clearance of lesions, and 70% of patients showed marked improvement of lesions. In a study conducted by Kar PK et al[85] showed PUVASOL showed complete clearance in 32% of patients, marked improvement in 44% of patients and poor response in 24% of patients.

15 % of the patients in PUVASOL group showed poor response to treatment in our study, where as in study conducted by Sadhan Kumar Ghosh et al [86] showed 60% of patients had poor response. They also showed that PUVASOL with methotrexate gives better results than PUVASOL therapy alone.

The mean number of exposure in PUVA group is 14.72 weeks and 18.97 weeks in PUVASOL group. This shows PUVASOL therapy takes long time to clear the lesion.

COMPARISION OF NBUVB WITH PUVASOL GROUP

In NBUVB group the mean baseline PASI score is 31.04 and mean PASI score at 16 weeks is 0.83. Therefore there is 97.9% reduction in PASI score at end of 16 weeks. In PUVASOL group the mean baseline PASI score is 31.59 and at mean PASI score at 16 weeks is 7.76. Therefore there is 75.44 % reduction in PASI score at end of 16 weeks.

From above data it is inferred that NBUVB showed better results in terms of clearance of lesions when compared to PUVASOL therapy after 16 weeks. The p value is <0.005 which is statistically significant.

So NBUVB therapy produces better clearance of lesions than PUVASOL therapy.

The mean number of exposure in NBUVB group is 14.88 weeks and 18.97 weeks in PUVASOL group. This shows PUVASOL therapy takes long time to clear the lesion.

POOR RESPONSE

Poor response was seen in 1 patient in NBUVB group and 3 patients in PUVASOL group. In PUVA group none had poor response. In our study it has no correlation with baseline PASI score.

SIDE EFFECTS

The adverse effects in our study were minimal. The common side effects were erythema, nausea, initial exacerbation and pruritis. The adverse effect profile observed in our study was similar to that reported in the literature.

Markham and Collins[86] in their study showed that both PUVA and NBUVB therapy are erythemogenic. They also reported that other side effects like nausea, headache, pruritis and alopecia were commonly observed in PUVA group. The above observation is similar to the present study.

Sadhan Kumar Ghosh et al[85] reported that erythema, nausea and vomiting were common side effect with PUASOL therapy. Our study also shows similar results.

Initial exacerbation was noted in 3 of our patients in NBUVB group, but newer lesions ceased to appear with continuation of therapy. This could be due to immunomodulatory effect of NBUVB.

Pruritis was noted in one of our patients in PUVA group which subsided with regular use of emollients and continuation of therapy. It is assumed to be related to prostaglandin release.

CONCLUSION

- PUVA therapy is an effective modality of treatment in chronic plaque type psoriasis.
- NBUVB therapy has equal efficacy to PUVA therapy in our study.
- The mean cumulative dose is almost equal for both PUVA and NBUVB therapy.
- However the mean number of exposure is less for PUVA group when compared to NBUVB group.
- When PUVA and NBUVB are compared there is no statistically significant difference in mean PASI score reduction at 16 weeks. The percentage of reduction of mean PASI at 16 weeks in PUVA group is 98.9% and in NBUVB group is 97.9%. So both are almost equally effective. But when duration of treatment is taken into account PUVA therapy scores over the NBUVB therapy.
- When PUVA and NBUVB therapy are compared with PUVASOL the rate of clearance of lesions in later group is poor.
- All the side effects noted in our study were minor and they were treated conservatively.

- In conclusion our study has shown that both PUVA and NBUVB groups achieved >75% or complete clearance at end of 16 weeks when compared to PUVASOL group. But PUVA group achieved faster clearance with less number of exposures as compared to NBUVB group.

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COMPARATIVE STUDY OF THERAPEUTIC EFFICACY OF PUVA, NBUVB AND PUVASOL IN THE TREATMENT OF CHRONIC PLAQUE TYPE PSORIASIS

PROFORMA

Name: Date:

Age: Op No:

Sex: Case No:

Occupation :

Address:

HISTORY:

Duration:

Itching: Yes: No:

H/O Previous treatment: Topical: Systemic:

EXACERBATION WITH:

1. Cold climate
2. Sunlight
6. Emotional factors
7. Pregnancy

3. Dialysis	8. Puberty
4. Infection	9. Menopause
5. Trauma	

PAST HISTORY:

Hypertension	Diabetes mellitus	Tuberculosis
Photosensitivity	Cutaneous malignancy	Radiotherapy

DRUG TAKEN FOR ANY OTHER CONDITION:

Yes **No**

If yes

Name of the drug:

Duration of treatment:

FAMILY HISTORY:

Father:	Mother:
Siblings:	Others:

No. OF CHILDREN:

Male:	**Female:**

PERSONAL HISTORY:

Smoking: **Alcohol:**

MENSTRUAL HISTORY:

PREGNANCY: **LACTATION:**

GENERAL EXAMINATION:

1. Pallor
2. Icterus
3. Edema
4. Pulse
5. Blood pressure
6. Weight

SYSTEMIC EXAMINATION:

CVS

RS

P/A

CNS

ENT

DENTAL

DERMATOLOGICAL EXAMINATION:

Skin lesions	**Site**
	Morphology
	Surface area involved
	Auspitz sign – yes/no
Mucous membrane	
Scalp	
Hair	
Nail	
Joint involvement	

AREA &SEVERITY ASSESSMENT BY PASI SCORING:

Erythema / Infiltration / Desquamation scoring	**Area scoring**
0- Nil	**0- Nil**
1- Mild	**1- 0-9%**
2- Moderate	**2- 10-29%**
3- Severe	**3- 30-49%**
4- Very severe	**4- 50-69%**
	5- 70-89%
	6- 90-100%

PASI was calculated as follows

PASI = 0.1(E_H+I_H+D_H) AH + 0.2(E_U+I_U+D_U) AU +

0.3(E_T+I_T+D_T) AT + 0.4(E_L+I_L+D_L)

A – Area **H – Head** **T – Trunk**

U – Upper limb **L - Limb**

INVESTIGATIONS:

Ophthalmological examination:

Total count:

Differential count:

ESR:

Hb:

Blood sugar:

Urea:

Creatinine:

Serum calcium:

Serum uric acid:

Blood VDRL:

HIV:

LFT:

PUVA CHART

Date	Cycle	Dose	Duration	Cumulative dose	Side effects

NBUVB CHART

Date	Cycle	Dose	Duration	Cumulative dose	Side effects

FOLLOW UP

Weeks	PASI score	Cumulative dose
0		
4		
8		
12		
16		

PUVA

S.No	AGE	SEX	DURATION	F/H	SCALP	MM	NAIL	JOINT	PASI 0	PASI 4	PASI 8	PASI 12	PASI 16	NO.OF EXPO	WEEKS OF EXPO	CD	SE
1	20	F	1 YEAR	N	Y	N	N	N	38	20.3	12	6.3	0	28	14	20.5	E
2	30	M	4 YEARS	N	Y	N	P,R,SUH	N	24	16.3	8.4	2.1	0.8	36	18	24	NA
3	30	M	3 MONTHS	N	N	N	N	N	27.6	10.2	2.7	0	0	20	10	25	E
4	45	M	1.5 MONTH	N	Y	N	N	N	40.8	32.6	16.4	10.5	2.1	42	21	27.5	BS
5	47	F	2 YEAR	N	N	N	P	N	28.4	20.4	12.6	2.2	0	26	13	19	NIL
6	32	M	1 YEAR	N	N	N	N	N	32.8	24.2	9.4	1.1	0	26	13	19	PR
7	32	M	6 MONTH	N	N	N	N	N	35.2	25.2	13.5	6.4	1.2	38	18	16	NIL
8	19	M	2 MONTH	N	N	N	N	N	18	9.4	1.2	0	0	18	9	15.5	NIL
9	56	F	2 YEARS	Y	Y	N	P	Y	32	23	8.6	1.2	0	26	13	19	NIL
10	42	F	1 YEAR	N	N	N	N	N	33.6	21.6	16.2	4.6	2.7	44	22	28	B.S
11	36	M	8 MONTH	N	N	N	N	N	43.5	28.8		DISCONTINUED					NIL
12	53	M	1.5 YEAR	N	Y	N	N	N	39	26.4		DISCONTINUED					NIL
13	21	M	7 MONTHS	Y	N	N	N	N	26.4	18.8	8.1	0	0	22	11	17.5	NIL
14	26	M	4 MONTHS	N	N	N	N	N	27	17.3	11.2	4.7	0	44	22	28	NA
15	50	MM	3 YEARS	N	Y	N	P,R,SUH	Y	42.3	31.1	21.4	9.6	0.1	34	17	23.5	B.S
16	45	F	2 YEARS	Y	N	N	P	N	44	24.6	14.3	4.2	0	30	15	21	NIL
17	61	M	4 YEARS	N	N	N	P	N	34.2	18.4	9.6	1.1	0	26	13	19	NIL
18	38	M	6 MONTHS	N	N	N	N	N	19.2	10.8	4.6	0	0	20	10	16.5	NIL
19	36	M	8 MONTHS	N	N	N	N	N	28.4	16.3	9.4	0	0	24	12	18.5	NIL
20	42	F	1 YEAR	N	N	N	N	N	29.6	19.4	10.1	3.3	0	28	14	20.5	E

NBUVB

S.No	AGE	SEX	DURATION	F/H	SCALP	MM	NAIL	JOINT	PASI 0	PASI 4	PASI 8	PASI 12	PASI 16	NO.OF EXPO	WEEKS OF EXPO	CD	SE
1	46	F	2 YEARS	N	N	N	SUH	N	19.2	10.8	2.4	1	0	45	15	17.25	NIL
2	33	M	2 MONTHS	N	Y	N	N	N	31.6	23.6	14.7	6.8	1.2	54	18	19.5	NIL
3	49	M	5 YEARS	N	N	N	P	N	27.6	10.2	2.7	0	0	30	10	13.5	NIL
4	55	M	6 YEARS	N	N	N	N	N	34.2	27.2	17.4	10.4	4.1	63	21	21.75	E
5	20	F	3 MONTHS	N	Y	N	P	N	31.5	28.1	19.4	7.6	0	42	14	16.5	NIL
6	21	M	1 YEAR	Y	N	N	N	N	39	26.4	10.8	4.2	0	42	14	16.5	NIL
7	28	F	3 YEARS	N	Y	N	P	N	40.8	35.6	21	9.6	2.1	57	19	20.25	E
8	23	M	6 MONTHS	N	N	N	P	N	15.2	10.1	1.5	0	0	30	10	13.5	NIL
9	29	F	2 YEARS	N	N	N	N	N	42	24.1	10.4	4.8	2.1	57	19	20.25	NIL
10	17	M	9 MONTHS	N	N	N	N	N	26.4	20.8	8.1	0	0	33	11	14.25	NIL
11	59	M	4 YEARS	Y	Y	N	SUH	Y	46.4	32.4	20.8	12.8	4.6	66	22	23.5	NIL
12	55	F	2 YEARS	N	Y	N	P	N	34.8	30.2	26.4	20.8		POOR RESPONSE			NIL
13	25	M	1 MONTH	N	N	N	N	N	19.2	10.8	4.6	0	0	30	10	13.5	NIL
14	63	M	8 MONTHS	N	Y	N	P	Y	21.2	18.4	12.6	8.2	0	42	14	16.5	IE
15	46	M	8 YEARS	N	Y	N	P	N	47.8	DISCONTINUED							NIL
16	28	M	2 MONTHS	N	N	N	N	N	30.2	15.2	10.4	4.2	0	42	14	16.5	NIL
17	49	M	6 MONTHS	N	N	N	N	N	31.2	16.5	7.2	1.3	0	39	13	15.75	NIL
18	40	M	3 YEARS	Y	Y	N	SUH	Y	24.9	14.7	7.4	3	0	45	15	15.25	IE
19	30	F	5 MONTHS	N	N	N	N	N	26	16.3	11.4	4.6	0	42	14	16.5	IE
20	45	F	6 MONTHS	N	N	N	N	N	31.6	24.2	18.4	13.2		POOR RESPONSE			NIL

PUVASOL

S.No	AGE	SEX	DURATION	F/H	SCALP	MM	NAIL	JOINT	PASI 0	PASI 4	PASI 8	PASI 12	PASI 16	NO.OF EXPO	WEEKS OF EXPO	SE
1	57	M	4 MONTHS	N	Y	N	N	Y	44	42.6	38.4	36.7	32.4	POOR	RESPONSE	NIL
2	34	F	1 YEAR	N	N	N	P	N	28.4	24.6	20.7	13.2	4.6	63	21	E
3	30	M	6 MONTHS	N	Y	N	N	N	31.8	26.8	19.4	11.3	3.1	60	20	NA
4	40	F	8 MONTHS	N	N	N	N	N	41.8	37.8	21.4	12.6	3.1	60	20	NIL
5	32	F	8 YESRS	N	N	N	N	N	36.8	24.8	18.4	12.2	4.1	63	21	E
6	45	F	2 YEARS	N	N	N	P	N	29.6	19.4	10.2	3.2	0	45	15	NIL
7	25	F	8 MONTHS	N	N	N	N	N	21.6	16.2	7.2	5.4	0.9	54	18	NIL
8	37	F	2 MONTHS	N	N	N	N	N	25.2	18	10.8	8.1	0	48	16	NIL
9	44	M	2 YEARS	N	N	N	P,SUH	Y	38.2		DISCONTINUED					NIL
10	35	M	4 MONTHS	N	N	N	N	N	36	34.8	32.4	30.6	28.3	POOR	RESPONSE	NIL
11	38	M	9 MONTHS	N	N	N	N	N	40.2	31.8	24.6	14.5	5.8	69	23	E
12	42	M	2 YEARS	Y	Y	N	P,SUH	Y	42.3	39.2	36.4	33.5	30.1	POOR	RESPONSE	NIL
13	58	M	5 MONTHS	N	N	N	N	N	21.6	15.2	6.2	3.4	0	48	16	NIL
14	32	F	1 YEAR	Y	N	N	N	N	28	15.8	11.4	6.3	1.1	57	19	NA
15	40	M	3 YEARS	N	N	N	P,SUH	Y	36	28.8	14.4	9	1.8	60	20	NIL
16	53	F	1.5 YEARS	N	N	N	N	N	35.2	26.4		DISCONTINUED				NIL
17	37	F	6 MONTHS	N	N	N	N	N	18.9	12.4	7.3	4.2	4.2	51	17	NIL
18	31	M	7 MONTHS	N	Y	N	P	N	21	18.6	11.4	7.3	7.3	60	20	NA
19	36	M	9 MONTHS	N	N	N	N	N	34.2	24.6	16.4	10.8	10.8	60	20	NIL
20	43	M	2 YEARS	Y	Y	N	P,R,SUH	N	21	16.4	11.8	2.1	2.1	54	18	NIL

KEY TO MASTER CHART

- M- MALE
- F- FEMALE
- F/H – FAMILY HISTORY
- MM- MUCOUS MEMBRANE INVOLVEMENT
- Y – YES
- N – NO
- P – PITTING
- R – RIDGING
- SUH – SUBUNGUAL HYPERKERATOSIS
- PASI – PSORIASIS AREA AND SEVERITY INDEX
- CD – CUMULATIVE DOSE
- SE – SIDE EFFECTS
- E – ERYTHEMA
- PR – PRURITIS
- NA – NAUSEA
- IE – INITIAL EXACERBATION

ABBREVIATIONS

- PUVA – PSORALEN ULTRAVIOLET A
- NBUVB – NARROW BAND ULTRAVIOLET B
- PUVASOL – PSORALEN ULTRAVIOLET SOLAR THERAPY
- PASI – PSORIASIS AREA AND SEVERITY SCORE
- MED – MINIMAL ERYTHEMA DOSE
- MPD – MINIMUM PHOTOTOXIC DOSE

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI -3

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CERTIFICATE OF APPROVAL

To
Dr. R. Akila
PG in MDDVL
Madras Medical College, Chennai -3

Dear Dr. R. Akila

The Institutional Ethics committee of Madras Medical College, reviewed and discussed your application for approval of the proposal entitled "Comparative study of therapeutic efficacy of puva, puvasol and narrow band UV-B in treatment of psoriasis" No. 10122011

The following members of Ethics Committee were present in the meeting held on 22.12.2011 conducted at Madras Medical College, Chennai -3.

1.	Prof. S.K. Rajan. MD	-- Chairperson
2.	Prof. R. Nandhini MD Director, Institute of Pharmacology ,MMC, Ch-3	-- Member
3	Prof. Pregna B. Dolia MD Director , Institute of Biochemistry, MMC, Ch-3	-- Member
4.	Prof. S. Regunanthan, MD Prof of Internal Medicine, MMC, Ch-3	-- Member
5.	Prof. Md Ali MD. DM Prof & Head , Dept. of MGE, MMC,Ch-3	-- Member
6.	Thiru. S. Govindsamy. BA BL	-- Lawyer

We approve the proposal to be conducted in its presented form.

Sd/ Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, and SAE occurring in the course of the study, any changes in the protocol and patients information / informed consent and asks to be provided a copy of the final report.

Member Secretary, Ethics Committee